

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 March 2002 (21.03.2002)

PCT

(10) International Publication Number
WO 02/022080 A3

(51) International Patent Classification⁷: C12N 15/86

(21) International Application Number: PCT/US01/28861

(22) International Filing Date:
14 September 2001 (14.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/233,180 15 September 2000 (15.09.2000) US

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
2 May 2002

Date of publication of the revised international search report:
16 January 2003

(48) Date of publication of this corrected version:
6 March 2003

(15) Information about Corrections:

see PCT Gazette No. 10/2003 of 6 March 2003, Section II

Previous Corrections:

see PCT Gazette No. 03/2003 of 16 January 2003, Section II

see PCT Gazette No. 30/2002 of 25 July 2002, Section II

[Continued on next page]

(54) Title: ENHANCED FIRST GENERATION ADENOVIRUS VACCINES EXPRESSING CODON OPTIMIZED HIV1-GAG, POL, NEF AND MODIFICATIONS

(57) Abstract: First generation adenoviral vectors and associated recombinant adenovirus-based HIV vaccines which show enhanced stability and growth properties and greater cellular-mediated immunity are described within this specification. These adenoviral vectors are utilized to generate and produce through cell culture various adenoviral-based HIV-1 vaccines which contain HIV-1 gag, HIV-1 pol and/or HIV-1 nef polynucleotide pharmaceutical products, and biologically relevant modifications thereof. These adenovirus vaccines, when directly introduced into living vertebrate tissue, preferably a mammalian host such as a human or non-human mammal of commercial or domestic veterinary importance, express the HIV1- Gag, Pol and/or Nef protein or biological modification thereof, inducing a cellular immune response which specifically recognizes HIV-1. The exemplified polynucleotides of the present invention are synthetic DNA molecules encoding HIV-1 Gag, encoding codon optimized HIV-1 Pol, derivatives of optimized HIV-1 Pol (including constructs wherein protease, reverse transcriptase, RNase H and integrase activity of HIV-1 Pol is inactivated), HIV-1 Nef and derivatives of optimized HIV-1 Nef, including nef mutants which effect wild type characteristics of Nef, such as myristylation and down regulation of host CD4. The adenoviral vaccines of the present invention, when administered alone or in a combined modality regime, will offer a prophylactic advantage to previously uninfected individuals and/or provide a therapeutic effect by reducing viral load levels within an infected individual, thus prolonging the asymptomatic phase of HIV-1 infection.

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TITLE OF THE INVENTION

ENHANCED FIRST GENERATION ADENOVIRUS VACCINES EXPRESSING
CODON OPTIMIZED HIV1-GAG, POL, NEF AND MODIFICATIONS

5 CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit, under 35 U.S.C. §119(e), of U.S.
provisional applications 60/233,180, 60/279,056, and Attorney Docket 20867PV2
(serial number unassigned), filed September 15, 2000, March 27, 2001, and
September 7, 2001, respectively.

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STATEMENT REGARDING FEDERALLY-SPONSORED R&D

Not Applicable

REFERENCE TO MICROFICHE APPENDIX

15

Not Applicable

FIELD OF THE INVENTION

The present invention relates to recombinant, replication-deficient first
generation adenovirus vaccines found to exhibit enhanced growth properties and
20 greater cellular-mediated immunity as compared to other replication-deficient vectors.
The invention also relates to the associated first generation adenoviral vectors
described herein, which, through the incorporation of additional 5' adenovirus
sequence, enhance large scale production efficiency of the recombinant, replication-
defective adenovirus described herein. Another aspect of the instant-invention is the
25 surprising discovery that the intron A portion of the human cytomegalovirus (hCMV)
promoter constitutes a region of instability in adenoviral vector constructs. Removal
of this region from adenoviral expression constructs results in greatly improved vector
stability. Therefore, improved vectors expressing a transgene under the control of an
intron A-deleted CMV promoter constitute a further aspect of this invention. These
30 adenoviral vectors are useful for generating recombinant adenovirus vaccines against
human immunodeficiency virus (HIV). In particular, the first generation adenovirus
vectors disclosed herein are utilized to construct and generate adenovirus-based HIV-
1 vaccines which contain HIV-1 Gag, HIV-1 Pol and/or HIV-1 Nef polynucleotide
pharmaceutical products, and biologically active modifications thereof. Host
35 administration of the recombinant, replication-deficient adenovirus vaccines described
herein results in expression of HIV-1 Gag, HIV-1- Pol and/or Nef protein or

immunologically relevant modifications thereof, inducing a cellular immune response which specifically recognizes HIV-1. The exemplified polynucleotides of the present invention are synthetic DNA molecules encoding codon optimized HIV-1 Gag, HIV-1 Pol, derivatives of optimized HIV-1 Pol (including constructs wherein protease, reverse transcriptase, RNase H and integrase activity of HIV-1 Pol is inactivated), HIV-1 Nef, and derivatives of optimized HIV-1 Nef, including nef mutants which effect wild type characteristics of Nef, such as myristylation and down regulation of host CD4. The HIV adenovirus vaccines of the present invention, when administered alone or in a combined modality and/or prime/boost regimen, will offer a prophylactic advantage to previously uninfected individuals and/or provide a therapeutic effect by reducing viral load levels within an infected individual, thus prolonging the asymptomatic phase of HIV-1 infection.

BACKGROUND OF THE INVENTION

Human Immunodeficiency Virus-1 (HIV-1) is the etiological agent of acquired human immune deficiency syndrome (AIDS) and related disorders. HIV-1 is an RNA virus of the Retroviridae family and exhibits the 5' LTR-*gag-pol-env*-LTR 3' organization of all retroviruses. The integrated form of HIV-1, known as the provirus, is approximately 9.8 Kb in length. Each end of the viral genome contains flanking sequences known as long terminal repeats (LTRs). The HIV genes encode at least nine proteins and are divided into three classes; the major structural proteins (Gag, Pol, and Env), the regulatory proteins (Tat and Rev); and the accessory proteins (Vpu, Vpr, Vif and Nef).

The *gag* gene encodes a 55-kilodalton (kDa) precursor protein (p55) which is expressed from the unspliced viral mRNA and is proteolytically processed by the HIV protease, a product of the *pol* gene. The mature p55 protein products are p17 (matrix), p24 (capsid), p9 (nucleocapsid) and p6.

The *pol* gene encodes proteins necessary for virus replication; a reverse transcriptase, a protease, integrase and RNase H. These viral proteins are expressed as a Gag-Pol fusion protein, a 160 kDa precursor protein which is generated via a ribosomal frame shifting. The viral encoded protease proteolytically cleaves the Pol polypeptide away from the Gag-Pol fusion and further cleaves the Pol polypeptide to the mature proteins which provide protease (Pro, P10), reverse transcriptase (RT, P50), integrase (IN, p31) and RNase H (RNase, p15) activities.

The *nef* gene encodes an early accessory HIV protein (Nef) which has been shown to possess several activities such as down regulating CD4 expression, disturbing T-cell activation and stimulating HIV infectivity.

5 The *env* gene encodes the viral envelope glycoprotein that is translated as a 160-kilodalton (kDa) precursor (gp160) and then cleaved by a cellular protease to yield the external 120-kDa envelope glycoprotein (gp120) and the transmembrane 41-kDa envelope glycoprotein (gp41). Gp120 and gp41 remain associated and are displayed on the viral particles and the surface of HIV-infected cells.

10 The *tat* gene encodes a long form and a short form of the Tat protein, a RNA binding protein which is a transcriptional transactivator essential for HIV-1 replication.

The *rev* gene encodes the 13 kDa Rev protein, a RNA binding protein. The Rev protein binds to a region of the viral RNA termed the Rev response element (RRE). The Rev protein promotes transfer of unspliced viral RNA from the nucleus
15 to the cytoplasm. The Rev protein is required for HIV late gene expression and in turn, HIV replication.

Gp120 binds to the CD4/chemokine receptor present on the surface of helper T-lymphocytes, macrophages and other target cells in addition to other co-receptor molecules. X4 (macrophage tropic) virus show tropism for CD4/CXCR4 complexes
20 while a R5 (T-cell line tropic) virus interacts with a CD4/CCR5 receptor complex. After gp120 binds to CD4, gp41 mediates the fusion event responsible for virus entry. The virus fuses with and enters the target cell, followed by reverse transcription of its single stranded RNA genome into the double-stranded DNA via a RNA dependent DNA polymerase. The viral DNA, known as provirus, enters the cell nucleus, where
25 the viral DNA directs the production of new viral RNA within the nucleus, expression of early and late HIV viral proteins, and subsequently the production and cellular release of new virus particles. Recent advances in the ability to detect viral load within the host shows that the primary infection results in an extremely high generation and tissue distribution of the virus, followed by a steady state level of virus
30 (albeit through a continual viral production and turnover during this phase), leading ultimately to another burst of virus load which leads to the onset of clinical AIDS. Productively infected cells have a half life of several days, whereas chronically or latently infected cells have a 3-week half life, followed by non-productively infected cells which have a long half life (over 100 days) but do not significantly contribute to
35 day to day viral loads seen throughout the course of disease.

Destruction of CD4 helper T lymphocytes, which are critical to immune defense, is a major cause of the progressive immune dysfunction that is the hallmark of HIV infection. The loss of CD4 T-cells seriously impairs the body's ability to fight most invaders, but it has a particularly severe impact on the defenses against viruses, fungi, parasites and certain bacteria, including mycobacteria.

Effective treatment regimens for HIV-1 infected individuals have become available recently. However, these drugs will not have a significant impact on the disease in many parts of the world and they will have a minimal impact in halting the spread of infection within the human population. As is true of many other infectious diseases, a significant epidemiologic impact on the spread of HIV-1 infection will only occur subsequent to the development and introduction of an effective vaccine. There are a number of factors that have contributed to the lack of successful vaccine development to date. As noted above, it is now apparent that in a chronically infected person there exists constant virus production in spite of the presence of anti-HIV-1 humoral and cellular immune responses and destruction of virally infected cells. As in the case of other infectious diseases, the outcome of disease is the result of a balance between the kinetics and the magnitude of the immune response and the pathogen replicative rate and accessibility to the immune response. Pre-existing immunity may be more successful with an acute infection than an evolving immune response can be with an established infection. A second factor is the considerable genetic variability of the virus. Although anti-HIV-1 antibodies exist that can neutralize HIV-1 infectivity in cell culture, these antibodies are generally virus isolate-specific in their activity. It has proven impossible to define serological groupings of HIV-1 using traditional methods. Rather, the virus seems to define a serological "continuum" so that individual neutralizing antibody responses, at best, are effective against only a handful of viral variants. Given this latter observation, it would be useful to identify immunogens and related delivery technologies that are likely to elicit anti-HIV-1 cellular immune responses. It is known that in order to generate CTL responses antigen must be synthesized within or introduced into cells, subsequently processed into small peptides by the proteasome complex, and translocated into the endoplasmic reticulum/Golgi complex secretory pathway for eventual association with major histocompatibility complex (MHC) class I proteins. CD8⁺ T lymphocytes recognize antigen in association with class I MHC via the T cell receptor (TCR) and the CD8 cell surface protein. Activation of naive CD8⁺ T cells into activated effector or memory cells generally requires both TCR engagement of antigen as described above as well as engagement of costimulatory proteins. Optimal

induction of CTL responses usually requires "help" in the form of cytokines from CD4⁺ T lymphocytes which recognize antigen associated with MHC class II molecules via TCR and CD4 engagement.

European Patent Applications 0 638 316 (Published February 15, 1995) and 0 586 076 (Published March 9, 1994), (both assigned to American Home Products Corporation) describe replicating adenovirus vectors carrying an HIV gene, including *env* or *gag*. Various treatment regimens were used with chimpanzees and dogs, some of which included booster adenovirus or protein plus alum treatments.

Replication-defective adenoviral vectors harboring deletions in the E1 region are known, and recent adenoviral vectors have incorporated the known packaging repeats into these vectors; e.g., see EP 0 707 071, disclosing, *inter alia*, an adenoviral vector deleted of E1 sequences from base pairs 459 to 3328; and U.S. Patent No. 6,033,908, disclosing, *inter alia*, an adenoviral vector deleted of base pairs 459-3510. The packaging efficiency of adenovirus has been taught to depend on the number of incorporated individual A (packaging) repeats; see, e.g., Gräble and Hearing, 1990 *J. Virol.* 64(5):2047-2056; Gräble and Hearing, 1992 *J. Virol.* 66(2):723-731.

Larder, et al., (1987, *Nature* 327: 716-717) and Larder, et al., (1989, *Proc. Natl. Acad. Sci.* 86: 4803-4807) disclose site specific mutagenesis of HIV-1 RT and the effect such changes have on *in vitro* activity and infectivity related to interaction with known inhibitors of RT.

Davies, et al. (1991, *Science* 252:, 88-95) disclose the crystal structure of the RNase H domain of HIV-1 Pol.

Schatz, et al. (1989, *FEBS Lett.* 257: 311-314) disclose that mutations Glu478Gln and His539Phe in a complete HIV-1 RT/RNase H DNA fragment results in defective RNase activity without effecting RT activity.

Mizrahi, et al. (1990, *Nucl. Acids. Res.* 18: pp. 5359-5353) disclose additional mutations Asp443Asn and Asp498Asn in the RNase region of the *pol* gene which also results in defective RNase activity. The authors note that the Asp498Asn mutant was difficult to characterize due to instability of this mutant protein.

Leavitt, et al. (1993, *J. Biol. Chem.* 268: 2113-2119) disclose several mutations, including a Asp64Val mutation, which show differing effect on HIV-1 integrase (IN) activity.

Wiskerchen, et al. (1995, *J. Virol.* 69: 376-386) disclose single and double mutants, including mutation of aspartic acid residues which effect HIV-1 IN and viral replication functions.

It would be of great import in the battle against AIDS to produce a prophylactic- and/or therapeutic-based HIV vaccine which generates a strong cellular immune response against an HIV infection. The present invention addresses and meets these needs by disclosing a class of adenovirus vaccines which, upon host administration, express codon optimized and modified versions of the HIV-1 genes, *gag*, *pol* and *nef*. These recombinant, replication-defective adenovirus vaccines may be administered to a host, such as a human, alone or as part of a combined modality regimen and/or prime-boost vaccination regimen with components of the present invention and/or a distinct viral HIV DNA vaccine, non-viral HIV DNA vaccine, HIV subunit vaccine, an HIV whole killed vaccine and/or a live attenuated HIV vaccine.

SUMMARY OF THE INVENTION

The present invention relates to enhanced replication-defective recombinant adenovirus vaccine vectors and associated recombinant, replication-deficient adenovirus vaccines which encode various forms of HIV-1 Gag, HIV-1 Pol, and/or HIV-1 Nef, including immunologically relevant modifications of HIV-1 Gag, HIV-1 Pol and HIV-1 Nef. The adenovirus vaccines of the present invention express HIV antigens and provide for improved cellular-mediated immune responses upon host administration. Potential vaccinees include but are not limited to primates and especially humans and non-human primates, and also include any non-human mammal of commercial or domestic veterinary importance. An effect of the improved recombinant adenovirus-based vaccines of the present invention should be a lower transmission rate to previously uninfected individuals (i.e., prophylactic applications) and/or reduction in the levels of the viral loads within an infected individual (i.e., therapeutic applications), so as to prolong the asymptomatic phase of HIV-1 infection. In particular, the present invention relates to adenoviral-based vaccines which encode various forms of codon optimized HIV-1 Gag (including but in no way limited to p55 versions of codon optimized full length (FL) Gag and tPA-Gag fusion proteins), HIV-1 Pol, HIV-1 Nef, and selected modifications of immunological relevance. The administration, intracellular delivery and expression of these adenovirus vaccines elicit a host CTL and Th response. The preferred replication-defective recombinant adenoviral vaccine vectors include but are not limited to synthetic DNA molecules which (1) encode codon optimized versions of wild type HIV-1 Gag; (2) encode codon optimized versions of HIV-1 Pol; (3) encode codon optimized versions of HIV-1 Pol fusion proteins; (4) encode codon optimized versions of modified HIV-1 Pol proteins and fusion proteins, including but not limited

to *pol* modifications involving residues within the catalytic regions responsible for RT, RNase and IN activity within the host cell; (5) encode codon optimized versions of wild type HIV-1 Nef; (6) codon optimized versions of HIV-1 Nef fusion proteins; and/or (7) codon optimized versions of HIV-1 Nef derivatives, including but not limited to *nef* modifications involving introduction of an amino-terminal leader sequence, removal of an amino-terminal myristylation site and/or introduction of dileucine motif mutations. The Nef-based fusion and modified proteins, disclosed within this specification and expressed from an adenoviral-based vector vaccine this specification, may possess altered trafficking and/or host cell function while retaining the ability to be properly presented to the host MHC I complex and in turn elicit a host CTL and Th response. Examples of HIV-1 Gag, Pol and/or Nef fusion proteins include but are not limited to fusion of a leader or signal peptide at the NH₂-terminal portion of the viral antigen coding region. Such a leader peptide includes but is not limited to a tPA leader peptide.

The adenoviral vector utilized in construction of the HIV-1 Gag-, HIV-1 Pol- and/or HIV-1 Nef- based vaccines of the present invention may comprise any replication-defective adenoviral vector which provides for enhanced genetic stability of the recombinant adenoviral genome through large scale production and purification of the recombinant virus. In other words, an HIV-1 Gag-, Pol- or Nef-based adenovirus vaccine of the present invention is a purified recombinant, replication-defective adenovirus which is shown to be genetically stable through multiple passages in cell culture and remains so during large scale production and purification procedures. Such a recombinant adenovirus vector and harvested adenovirus vaccine lends itself to large scale dose filling and subsequent worldwide distribution procedures which will be demanded of an efficacious monovalent or multivalent HIV vaccine. The present invention meets this basic requirement with description of a replication-defective adenoviral vector and vectors derived therefrom, at least partially deleted in E1, comprising a wildtype adenovirus *cis*-acting packaging region from about base pair 1 to between from about base pair 342 (more preferably, 400) to about base pair 458 of the wildtype adenovirus genome. A preferred embodiment of the instant invention comprises base pairs 1-450 of a wildtype adenovirus. In other preferred embodiments, the replication-defective adenoviral vector has, in addition thereto, a region 3' to the E1-deleted region comprising base pairs 3511-3523. Basepairs 342-450 (more particularly, 400-450) constitute an extension of the 5' region of previously disclosed vectors carrying viral antigens, particularly HIV antigens (see, e.g., PCT International Application PCT/US00/18332, published

January 11, 2001 (WO 01/02067), which claims priority to U.S. Provisional Application Serial Nos. 60/142,631 and 60/148,981, filed 7/6/1999 and 8/13/1999, respectively; these documents herein incorporated by reference. Applicants have found that extending the 5' region further into the E1 gene into the disclosed vaccine
5 vectors incorporated elements found to be important in optimizing the packaging of the virus.

As compared to previous vectors not comprising basepairs from about 1 to between from about base pair 342 (more preferably, 400) to about base pair 458 of the wildtype adenovirus genome, vectors comprising the above region exhibited enhanced
10 growth characteristics, with approximately 5-10 fold greater amplification rates, a more potent virus effect, allowing lower doses of virus to be used to generate equivalent immunity; and a greater cellular-mediated immune response than replication-deficient vectors not comprising this region (basepairs 1-450). Even more
15 important, adenoviral constructs derived therefrom are very stable genetically in large-scale production, particularly those comprising an expression cassette under the control of a hCMV promoter devoid of intron A. This is because Applicants have surprisingly found that the intron A portion of the hCMV promoter constituted a
20 region of instability when employed in adenoviral vectors. Applicants have, therefore, identified an enhanced adenoviral vector which is particularly suited for use in gene therapy and nucleotide-based vaccine vectors which, favorably, lends itself to large scale propagation.

A preferred embodiment of this invention is a replication-defective adenoviral vector in accordance with the above description wherein the gene is inserted in the form of a gene expression cassette comprising (a) a nucleic acid encoding a protein or
25 biologically active and/or immunologically relevant portion thereof; (b) a heterologous promoter operatively linked to the nucleic acid of part a); and, (c) a transcription terminator.

In preferred embodiments, the E1 gene, other than that contained within basepairs 1-450 or, alternatively, that contained within base pairs 1-450 and 3511-
30 3523 has been deleted from the adenoviral vector, and the gene expression cassette has replaced the deleted E1 gene. In other preferred embodiments, the replication defective adenovirus genome does not have a functional E3 gene, or the E3 gene has been deleted. Most preferably, the E3 region is present within the adenoviral genome. Further preferred embodiments are wherein the gene expression cassette is in an E1
35 anti-parallel (transcribed in a 3' to 5' direction relative to the vector backbone)

orientation or, more preferably, an E1 parallel (transcribed in a 5' to 3' direction relative to the vector backbone) orientation.

Further embodiments relate to a shuttle plasmid vector comprising: an adenoviral portion and a plasmid portion, wherein said adenovirus portion comprises:

- 5 a) a replication defective adenovirus genome, at least partially deleted in E1, comprising a wildtype adenovirus *cis*-acting packaging region from about base pair 1 to between from about base pair 342 (more preferably, 400) to about base pair 458 (preferably, 1-450) of the wildtype adenovirus genome and, preferably, in addition thereto, basepairs 3511-3523 of a wildtype adenovirus sequence; and b) a gene
10 expression cassette comprising: (a) a nucleic acid encoding a protein or biologically active and/or immunologically relevant portion thereof; (b) a heterologous promoter operatively linked to the nucleic acid of part a); and (c) a transcription terminator and/or a polyadenylation site.

- Other aspects of this invention include a host cell comprising said adenoviral
15 vectors and/or said shuttle plasmid vectors; vaccine compositions comprising said vectors; and methods of producing the vectors comprising (a) introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and (b) harvesting the resultant adenoviral vectors.

- To this end, the present invention particularly relates to harvested
20 recombinant, replication defective virus derived from a host cell, such as but not limited to 293 cells or PER.C6[®] cells, including but not limited to harvested virus related to any of the MRKAd5 vector backbones, with or without an accompanying transgene, including but not limited to the HIV-1 antigens described herein. An HIV-1 vaccine is represented by any harvested, recombinant adenovirus material
25 which expresses any one or more of the HIV-1 antigens disclosed herein. This harvested material may then be purified, formulated and stored prior to host administration.

- Another aspect of this invention is a method of generating a cellular immune response against a protein in an individual comprising administering to the individual
30 an adenovirus vaccine vector comprising:

- a) a recombinant, replication defective adenoviral vector, at least partially deleted in E1, comprising a wildtype adenovirus *cis*-acting adenovirus packaging region from about base pair 1 to between from about base pair 342 (more preferably, 400) to about base pair 458 (preferably, 1-450) and, preferably in addition thereto,
35 base pairs 3511-3523 of a wildtype adenovirus sequence, and,

b) a gene expression cassette comprising: (i) a nucleic acid encoding a protein or biologically active and/or immunologically relevant portion thereof; (ii) a heterologous promoter operatively linked to the nucleic acid of part a); and (iii) a transcription terminator and/or a polyadenylation site.

5 In view of the efficacious nature of the adenoviral and/or DNA plasmid vaccines described herein, the present invention relates to all methodology regarding administration of one or more of these adenoviral and/or DNA plasmid vaccines to provide effective immunoprophylaxis, to prevent establishment of an HIV-1 infection following exposure to this virus, or as a post-HIV infection therapeutic vaccine to
10 mitigate the acute HIV-1 infection so as to result in the establishment of a lower virus load with beneficial long term consequences. As discussed herein, such a treatment regimen may include a monovalent or multivalent composition, various combined modality applications, and/or a prime/boost regimen to as to optimize antigen expression and a concomitant cellular-mediated and/or humoral immune response
15 upon inoculation into a living vertebrate tissue. Therefore, the present invention provides for methods of using the adenoviral and/or DNA plasmid vaccines disclosed herein within the various parameters disclosed herein as well as any additional parameters known in the art, which, upon introduction into mammalian tissue induces intracellular expression of the gag, pol and/or nef-based vaccines.

20 To this end, the present invention relates in part to methods of generating a cellular immune response in a vaccinee, preferably a human vaccinee, wherein the individual is given more than one administration of adenovirus vaccine vector, and it may be given in a regimen accompanied by the administration of a plasmid vaccine. The plasmid vaccine (also referred to herein as a "DNA plasmid vaccine" or "vaccine
25 plasmid" comprises a nucleic acid encoding a protein or an immunologically relevant portion thereof, a heterologous promoter operably linked to the nucleic acid sequence, and a transcription terminator or a polyadenylation signal (such as bGH or SPA, respectively). There may be a predetermined minimum amount of time separating the administrations. The individual can be given a first dose of plasmid vaccine, and then
30 a second dose of plasmid vaccine. Alternatively, the individual may be given a first dose of adenovirus vaccine, and then a second dose of adenovirus vaccine. In other embodiments, the plasmid vaccine is administered first, followed after a time by administration of the adenovirus vaccine. Conversely, the adenovirus vaccine may be administered first, followed by administration of plasmid vaccine after a time. In
35 these embodiments, an individual may be given multiple doses of the same adenovirus serotype in either viral vector or plasmid form, or the virus may be of

differing serotypes. In the alternative, a viral antigen of interest can be first delivered via a viral vaccine other than an adenovirus-based vaccine, and then followed with the adenoviral vaccine disclosed. Alternative viral vaccines include but are not limited to pox virus and venezuelan equine encephalitis virus.

5 The present invention also relates to multivalent adenovirus vaccine compositions which comprise Gag, Pol and Nef components described herein; see, e.g., Example 29 and Table 25. Such compositions will provide for an enhanced cellular immune response subsequent to host administration, particularly given the genetic diversity of human MHCs and of circulating virus. Examples, but not
10 limitations, include MRKAd5-vector based multivalent vaccine compositions which provide for a divalent (i.e., gag and nef, gag and pol, or pol and nef components) or a trivalent vaccine (i.e., gag, pol and nef components) composition. Such a multivalent vaccine may be filled for a single dose or may consist of multiple inoculations of each individually filled component; and may in addition be part of a prime/boost regimen
15 with viral or non-viral vector vaccines as introduced in the previous paragraph. To this end, preferred compositions are MRKAd5 adenovirus used in combination with multiple, distinct HIV antigen classes. Each HIV antigen class is subject to sequence manipulation, thus providing for a multitude of potential vaccine combinations; and such combinations are within the scope of the present invention. The utilization of
20 such combined modalities vaccine formulation and administration increase the probability of eliciting an even more potent cellular immune response when compared to inoculation with a single modality regimen.

 The concept of a "combined modality" as disclosed herein also covers the alternative mode of administration whereby multiple HIV-1 viral antigens may be
25 ligated into a proper shuttle plasmid for generation of a pre-adenoviral plasmid comprising multiple open reading frames. For example, a trivalent vector may comprise a gag-pol-nef fusion, in either a E3(-) or E3(+) background, preferably a E3 deleted backbone, or possibly a "2+1" divalent vaccine, such as a gag-pol fusion (i.e., codon optimized p55 gag and inactivated optimized pol; Example 29 and Table 25)
30 within the same MRKAd5 backbone, with each open reading frame being operatively linked to a distinct promoter and transcription termination sequence. Alternatively, the two open reading frames may be operatively linked to a single promoter, with the open reading frames operatively linked by an internal ribosome entry sequence (IRES). Therefore, a multivalent vaccine delivered as a single, or possibly a second
35 harvested recombinant, replication-deficient adenovirus is contemplated as part of the present invention.

Therefore, the adenoviral vaccines and plasmid DNA vaccines of this invention may be administered alone, or may be part of a prime and boost administration regimen. A mixed modality priming and booster inoculation scheme will result in an enhanced immune response, particularly if pre-existing anti-vector immune responses are present. This one aspect of this invention is a method of priming a subject with the plasmid vaccine by administering the plasmid vaccine at least one time, allowing a predetermined length of time to pass, and then boosting by administering the adenoviral vaccine. Multiple primings typically, 1-4, are usually employed, although more may be used. The length of time between priming and boost may typically vary from about four months to a year, but other time frames may be used. In experiments with rhesus monkeys, the animals were primed four times with plasmid vaccines, then were boosted 4 months later with the adenoviral vaccine. Their cellular immune response was notably higher than that of animals which had only received adenoviral vaccine. The use of a priming regimen may be particularly preferred in situations where a person has a pre-existing anti-adenovirus immune response.

It is an object of the present invention to provide for enhanced replication-defective recombinant adenoviral vaccine vector backbones. These recombinant adenoviral backbones may accept one or more transgenes, which may be passaged through cell culture for growth, amplification and harvest.

It is a further object to provide for enhanced replication-defective recombinant adenoviral vaccine vectors which encode various transgenes.

It is also an object of the present invention to provide for a harvested recombinant, replication-deficient adenovirus which shows enhanced growth and amplification rates while in combination with increased virus stability after continuous passage in cell culture. Such a recombinant adenovirus is particularly suited for use in gene therapy and nucleotide-based vaccine vectors which, favorably, lends itself to large scale propagation.

To this end, it is an object of the present invention to provide for (1) enhanced replication-defective recombinant adenoviral vaccine vectors as described herein which encode various forms of HIV-1 Gag, HIV-1 Pol, and/or HIV-1 Nef, including immunologically relevant modifications of HIV-1 Gag, HIV-1 Pol and HIV-1 Nef, and (2) harvested, purified recombinant replication-deficient adenovirus generated by passage of the adenoviral vectors of (1) through one or multiple passages through cell culture, including but not limited to passage through 293 cells or PER.C6® cells.

It is also an object of the present invention to provide for recombinant adenovirus harvested by one or multiple passages through cell culture. As relating to recombinant adenoviral vaccine vector, this recombinant virus is harvested and formulated for subsequent host administration.

5 It is also an object of the present invention to provide for replication-defective adenoviral vectors wherein at least one gene is inserted in the form of a gene expression cassette comprising (a) a nucleic acid encoding a protein or biologically active and/or immunologically relevant portion thereof; (b) a heterologous promoter operatively linked to the nucleic acid of part a); and, (c) a transcription terminator.

10 It is also an object of the present invention to provide for a host cell comprising said adenoviral vectors and/or said shuttle plasmid vectors; vaccine compositions comprising said vectors; and methods of producing the vectors comprising (a) introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and (b) harvesting the resultant adenoviral vectors.

15 It is a further object of the present invention to provide for methods of generating a cellular immune response against a protein in an individual comprising administering to the individual an adenovirus vaccine vector comprising a) a replication defective adenoviral vector, at least partially deleted in E1, comprising a wildtype adenovirus *cis*-acting packaging region from about base pair 1 to between from about base pair
20 342 (more preferably, 400) to about 450 (preferably, 1-450) and, preferably, 3511-3523 of a wildtype adenovirus sequence, and, b) a gene expression cassette comprising: (i) a nucleic acid encoding a protein or biologically active and/or immunologically relevant portion thereof; (ii) a heterologous promoter operatively linked to the nucleic acid of part a); and (iii) a transcription terminator and/or a
25 polyadenylation site.

It is also an object of the present invention to provide various alternatives for vaccine administration regimes, namely administration of one or more adenoviral and/or DNA plasmid vaccines described herein to provide effective immunoprophylaxis for uninfected individuals or a therapeutic treatment for HIV
30 infected patients. Such processes include but are not limited to multivalent HIV-1 vaccine compositions, various combined modality regimes as well as various prime/boost alternatives. These methods of administration, relating to vaccine composition and/or scheduled administration, will increase the probability of eliciting an even more potent cellular immune response when compared to inoculation with a
35 single modality regimen.

As used throughout the specification and claims, the following definitions and abbreviations are used:

"HAART" refers to -- highly active antiretroviral therapy --.

"first generation" vectors are characterized as being replication-defective.

- 5 They typically have a deleted or inactivated E1 gene region, and preferably have a deleted or inactivated E3 gene region as well.

"AEX" refers to Anion Exchange chromatography.

"QPA" refers to Quick PCR-based Potency Assay.

"bps" refers to basepairs.

- 10 "s" or "str" denotes that the transgene is in the E1 parallel or "straight" orientation.

"PBMCs" refers to peripheral blood monocyte cells.

"FL" refers to full length.

"FLgag" refers to a full-length optimized gag gene, as shown in Figure 2.

- 15 "Ad5-FLgag" refers to an adenovirus serotype 5 replication deficient virus which carries an expression cassette which comprises a full length optimized gag gene under the control of a CMV promoter.

- "Promoter" means a recognition site on a DNA strand to which an RNA polymerase binds. The promoter forms an initiation complex with RNA polymerase to initiate and drive transcriptional activity. The complex can be modified by activating sequences such as enhancers or inhibiting sequences such as silencers.

"Leader" means a DNA sequence at the 5' end of a structural gene which is transcribed along with the gene. This usually results a protein having an N-terminal peptide extension, often referred to as a pro-sequences.

- 25 "Intron" means a section of DNA occurring in the middle of a gene which does not code for an amino acid in the gene product. The precursor RNA of the intron is excised and is therefore not transcribed into mRNA not translated into protein.

- "Immunologically relevant" or "biologically active" means (1) with regards to a viral protein, that the protein is capable, upon administration, of eliciting a measurable immune response within an individual sufficient to retard the propagation and/or spread of the virus and/or to reduce the viral load present within the individual; or (2) with regards to a nucleotide sequence, that the sequence is capable of encoding for a protein capable of the above.

- 35 "Cassette" refers to a nucleic acid sequence which is to be expressed, along with its transcription and translational control sequences. By changing the cassette, a vector can express a different sequence.

"bGHpA" refers to the bovine growth hormone transcription terminator/polyadenylation sequence.

"tPAgag" refers to a fusion between the leader sequence of the tissue plasminogen activator leader sequence and an optimized HIV gag gene, as
5 exemplified in Figure 30A-B, whether in a DNA or adenovirus-based vaccine vector.

Where utilized, "IA" or "inact" refers to an inactivated version of a gene (e.g. IApol).

"MCS" is "multiple cloning site".

In general, adenoviral constructs, gene constructs are named by reference to
10 the genes contained therein. For example:

"Ad5 HIV-1 gag", also referred to as the original HIV-1 gag adenoviral vector, is a vector containing a transgene cassette composed of a hCMV intron A promoter, the full length version of the human codon-optimized HIV-1 gag gene, and the bovine growth hormone polyadenylation signal. The transgene was inserted in the
15 E1 antiparallel orientation in an E1 and E3 deleted adenovector.

"MRK Ad5 HIV-1 gag" also referred to as "MRKAd5gag" or "Ad5gag2" is an adenoviral vector taught herein which is deleted of E1, comprises basepairs 1-450 and 3511-3523, and has a human codon-optimized HIV-1 gene in an E1 parallel orientation under the control of a CMV promoter without intron A. The construct
20 also comprises a bovine growth hormone polyadenylation signal.

"pV1JnsHIVgag", also referred to as "HIVFLgagPR9901", is a plasmid comprising the CMV immediate-early (IE) promoter and intron A, a full-length codon-optimized HIV gag gene, a bovine growth hormone-derived polyadenylation and transcriptional termination sequence, and a minimal pUC backbone.

25 "pV1JnsCMV(no intron)-FLgag-bGHpA" is a plasmid derived from pV1JnsHIVgag which is deleted of the intron A portion of CMV and which comprises the full length HIV gag gene. This plasmid is also referred to as "pV1JnsHIVgag-bGHpA", pV1Jns-hCMV-FL-gag-bGHpA" and "pV1JnsCMV(no intron) + FLgag + bGHpA".

30 "pV1JnsCMV(no intron)-FLgag-SPA" is a plasmid of the same composition as pV1JnsCMV(no intron)-FLgag-bGHpA except that the SPA termination sequence replaces that of bGHpA. This plasmid is also referred to as "pV1Jns-HIVgag-SPA" and pV1Jns-hCMV-FLgag-SPA".

35 "pdelE1sp1A" is a universal shuttle vector with no expression cassette (i.e., no promoter or polyA). The vector comprises wildtype adenovirus serotype 5 (Ad5) sequences from bp 1 to bp 341 and bp 3524 to bp 5798, and has a multiple cloning

site between the Ad5 sequences ending 341 bp and beginning 3524 bp. This plasmid is also referred to as the original Ad 5 shuttle vector.

"MRKpdeIE1sp1A" or "MRKpdeIE1(Pac/pIX/pack450)" or "MRKpdeIE1(Pac/pIX/pack450)Cla1" is a universal shuttle vector with no expression cassette (i.e. no promoter or polyA) comprising wildtype adenovirus serotype 5 (Ad5) sequences from bp1 to bp450 and bp 3511 to bp 5798. The vector has a multiple cloning site between the Ad5 sequence ending 450 bp and beginning 3511 bp. This shuttle vector may be used to insert the CMV promoter and the bGHpA fragments in both the straight ("str". or E1 parallel) orientation or in the opposite (opp. or E1 antiparallel) orientation)

"MRKpdeIE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.)" is still another shuttle vector which is the modified vector that contains the CMV promoter (no intronA) and the bGHpA fragments. The expression unit containing the hCMV promoter (no intron A) and the bovine growth hormone polyadenylation signal has been inserted into the shuttle vector such that insertion of the gene of choice at a unique *Bgl*III site will ensure the direction of transcription of the transgene will be Ad5 E1 parallel when inserted into the MRKpAd5(E1/E3+)Cla1 pre-plasmid. This shuttle vector, as shown in Figures 22 and 23, was used to insert the respective IAPol and G2A,LLAA nef genes directly into.

"MRKpdeIE1-CMV(no intron)-FLgag-bGHpA" is a shuttle comprising Ad5 sequences from basepairs 1-450 and 3511-5798, with an expression cassette containing human CMV without intron A, the full-length human codon-optimized HIV gag gene and bovine growth hormone polyadenylation signal. This plasmid is also referred to as "MRKpdeIE1 shuttle +hCMV-FL-gag-BGHpA"

"MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA" is an adenoviral vector comprising all Ad5 sequences except those nucleotides encompassing the E1 region (from 451-3510), a human CMV promoter without intron A, a full-length human codon-optimized HIV gag gene, and a bovine growth hormone polyadenylation signal. This vector is also referred to as "MRKpAdHVE3 + hCMV-FL-gag-BGHpA", "MRKpAd5HIV-1gag", "MRKpAd5gag", "pMRKAd5gag" or "pAd5gag2".

"pV1Jns-HIV-pol inact(opt)" or "pV1Jns-HIV IA pol (opt)" is the inactivated Pol gene (contained within SEQ ID NO:3) cloned into the *Bgl*III site of V1Jns (Figure 17A-C). As noted herein, various derivatives of HIV-1 pol may be cloned into a plasmid expression vector such as V1Jns or V1Jns-tPA, thus serving directly as DNA vaccine candidates or as a source for subcloning into an appropriate adenoviral vector.

"MRKpdel+hCMVmin+FL-pol+bGHpA(s)" is the "MRKpdelE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.)" shuttle mentioned above which contains the IA pol gene in the proper orientation. This shuttle vector is used in a bacterial recombination with MRKpAd(E1-/E3+)Cla1.

5 "MRKpAd+hCMVmin+FL-pol+bGHpA(S)E3+", also referred to herein as "pMRKAd5pol", is the pre-adenovirus plasmid which comprises a CMV-pol inact(opt)-pGHpA construct. The construction of this pre-adenovirus plasmid is shown in Figure 22.

10 "pV1Jns/nef (G2A,LLAA)" or "V1Jns/opt nef (G2A,LLAA)" comprises codon optimized HIV-1 Nef wherein the open reading frame codes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175 (SEQ ID NO:13; which comprises an initiating methionine residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides 660-662). This fragment is subcloned into the Bgl II site of V1Jns
15 and/or V1Jns-tPA (Figures 16A-B). As noted above for HIV-1 pol, HIV-1 nef constructs may be cloned into a plasmid expression vector such as V1Jns or V1Jns-tPA, thus serving directly as DNA vaccine candidates or as a source for subcloning into an appropriate adenoviral vector.

"MRKpdelE1hCMVminFL-nefBGHpA(s)", also referred to herein as
20 "pMRKAd5nef", is the pre-adenovirus plasmid which comprises a CMV-nef (G2A,LLAA) codon optimized sequence. The construction of this pre-adenovirus plasmid is shown in Figure 23.

BRIEF DESCRIPTION OF THE FIGURES

25 Figure 1 shows the original HIV-1 gag adenovector (Ad5HIV-1gag). This vector is disclosed in PCT International Application No. PCT/US00/18332 (WO 01/02607) filed July 3, 2000, claiming priority to U.S. Provisional Application Serial No. 60/142,631, filed July 6, 1999 and U.S. Application Serial No. 60/148,981, filed August 13, 1999, all three applications which are hereby incorporated by reference.

30 Figure 2 shows the nucleic acid sequence (SEQ ID NO: 29) of the optimized human HIV-1 gag open reading frame.

Figure 3 shows diagrammatically the new transgene constructs in comparison with the original gag transgene.

Figure 4 shows the modifications made to the original adenovector backbone
35 in the generation of the novel vectors of the instant invention.

Figure 5 shows the virus mixing experiments that were carried out to determine the effects of the addition made to the packaging signal region (Expt. #1) and the E3 gene on viral growth (Expt. #2). The bars denote the region of modifications made to the E1 deletion.

5 Figure 6 shows an autoradiograph of viral DNA analysis following the viral mixing experiments described in Examples 6 and 7.

Figures 7A, 7B and 7C are as follows: Figure 7A shows the hCMV-Flagg-bGHpA adenovectors constructed within the MRKpAdHVE3 and MRKpAdHVO adenovector backbones. Both E1 parallel and E1 antiparallel transgene orientation are represented. Figure 7B shows the hCMV-Flagg-SPA adenovectors constructed within the MRKpAdHVE3 and MRKpAdHVO adenovector backbones. Again, both E1 parallel and E1 antiparallel transgene orientation are represented. Figure 7C shows the mCMV-Flagg-bGHpA adenovectors constructed within the MRKpAdHVE3 and MRKpAdHVO adenovector backbones. Once again, both E1 parallel and E1 antiparallel transgene orientation are represented.

15 Figure 8A shows the experiment designed to test the effect of transgene orientation.

Figure 8B shows the experiments designed to test the effect of polyadenylation signal.

20 Figure 9 shows viral DNA from the four adenoviral vectors tested (Example 12) at P5, following *Bst*E11 digestion.

Figure 10 shows viral DNA analysis of passages 11 and 12 of MRKpAdHVE3, MRKAd5HIV-1gag, and MRKAd5HIV-1gagE3-.

25 Figure 11 shows viral DNA analysis (*Hind*III digestion) of passage 6 MRKpAdHVE3 and MRKAd5HIV-1gag used to initiate the viral competition study. The last two lanes are passage 11 analysis of duplicate passages of the competition study (each virus at MOI of 280 viral particles).

Figure 12 shows viral DNA analysis by *Hind* III digestion on high passage numbers for MRKAd5HIV-1gag in serum-containing media with collections made at specified times. The first lane shows the 1kb DNA size marker. The other lanes represent pre-plasmid control (digested with *Pac*I and *Hind*III), MRKAd5HIV-1gag at P16, P19, and P21.

35 Figure 13 shows serum anti-p24 levels at 3 wks post i.m. immunization of balb/c mice (n=10) with varying doses of several Adgag constructs: (A) MRK Ad5 HIV-1 gag (through passage 5); (B) MRKAd5 hCMV-FLgag-bGHpA (E3-); (C) MRKAd5 hCMV-FLgag-SPA (E3+); (D) MRKAd5 mCMV-FLgag-bGHpA (E3+);

(E) research lot (293 cell-derived) of Ad5HIV-1 gag; and (F) clinical lot (Ad5gagFN0001) of Ad5HIV-1 gag. Reported are the geometric mean titers (GMT) for each cohort along with the standard error bars.

Figure 14 shows a restriction map of the pMRKAd5HIV-1gag vector.

5 Figures 15A-X illustrates the nucleotide sequence of the pMRKAd5HIV-1gag vector (SEQ ID NO:27.[coding] and SEQ ID NO:28 [non-coding]).

Figures 16A-B shows a schematic representation of DNA vaccine expression vectors V1Jns (A) and V1Jns-tPA (B), which are utilized for HIV-1 gag, pol and nef constructs in various DNA/viral vector combined modality regimens as disclosed
10 herein.

Figures 17A-C shows the nucleotide (SEQ ID NO:3) and amino acid sequence (SEQ ID NO:4) of IA-Pol. Underlined codons and amino acids denote mutations, as listed in Table 1.

Figure 18 shows codon optimized nucleotide and amino acid sequences
15 through the fusion junction of tPA-pol inact(opt) (contained within SEQ ID NOs: 7 and 8, respectively). The underlined portion represents the NH₂-terminal region of IA-Pol.

Figures 19A-B show a nucleotide sequence comparison between wild type nef(jrfl) and codon optimized nef. The wild type nef gene from the jrfl isolate
20 consists of 648 nucleotides capable of encoding a 216 amino acid polypeptide. WT, wild type sequence (SEQ ID NO:19); opt, codon-optimized sequence (contained within SEQ ID NO:1). The Nef amino acid sequence is shown in one-letter code (SEQ ID NO:2).

Figures 20A-C show nucleotide sequences at junctions between nef coding
25 sequence and plasmid backbone of nef expression vectors V1Jns/nef (Figure 20A), V1Jns/nef(G2A,LLAA) (Figure 20B), V1Jns/tpanef (Figure 20C) and V1Jns/tpanef(LLAA) (Figure 20C, also). 5' and 3' flanking sequences of codon optimized nef or codon optimized nef mutant genes are indicated by bold/italic letters; nef and nef mutant coding sequences are indicated by plain letters. Also indicated (as
30 underlined) are the restriction endonuclease sites involved in construction of respective nef expression vectors. V1Jns/tpanef and V1Jns/tpanef(LLAA) have identical sequences at the junctions.

Figure 21 shows a schematic presentation of nef and nef derivatives. Amino acid residues involved in Nef derivatives are presented. Glycine 2 and Leucine174
35 and 175 are the sites involved in myristylation and dileucine motif, respectively. For both versions of the tpanef fusion genes, the putative leader peptide cleavage sites are

indicated with "*", and a exogenous serine residue introduced during the construction of the mutants is underlined.

Figure 22 shows diagrammatically the construction of the pre-adenovirus plasmid construct, MRKAd5Pol.

5 Figure 23 shows diagrammatically the construction of the pre-adenovirus plasmid construct, MRKAd5Nef.

Figure 24 shows a comparison of clade B vs. clade C anti-gag T cell responses in clade B HIV-infected subjects.

10 Figure 25 shows a comparison of clade B vs. clade C anti-nef T cell responses in clade B HIV-infected subjects.

Figures 26A-AO illustrates the nucleotide sequence of the pMRKAd5HIV-1pol adenoviral vector (SEQ ID NO:32 [coding] and SEQ ID NO:33 [non-coding]), comprising the coding region of the inactivated pol gene (SEQ ID NO3).

15 Figures 27A-AM illustrates the nucleotide sequence of the pMRKAd5HIV-1 nef adenoviral vector (SEQ ID NO:34 [coding] and SEQ ID NO:35 [non-coding]), comprising the coding region of the inactivated pol gene (SEQ ID NO13).

Figure 28 shows the stability of MRKAd5 vectors comprising various promoter fragments (hCMV or mCMV) and terminations signals (bGH or SPA) in E3(+) or E3(-) backbones.

20 Figures 29A and B shows the anion-exchange HPLC viral particle concentrations of the freeze-thaw recovered cell associated virus at the 24, 36, 48, and 60 hpi time points (Figure 29A) and the timcourse QPA supernatant titers (Figure 29B) for MRKAd5gag, MRKAd5pol and MRKAd5nef.

25 Figure 30 shows the nucleotide sequence (SEQ ID NO:36) and amino acid sequence (SEQ ID NO:37) comprising the open reading frame of a representative tPA-gag fusion for use in the DNA and/or adenoviral vaccine disclosed herein.

30 Figure 31 shows the intracellular γ IFN staining of PBMCs collected at week 10 (post DNA prime) and week 30 (post Ad boost). The cells were stimulated overnight in the presence or absence of the gag peptide pool. They were subsequently stained using fluorescence-tagged anti-CD3, anti-CD8, anti-CD4, and anti- γ IFN monoclonal antibodies. Each plot shows all CD3+ T cells which were segregated in terms of positive staining for surface CD8 and γ IFN production. The numbers in the upper right and lower right quadrants of each plot are the percentages of CD3+ cells that were CD8+ γ IFN+ and CD4+ γ IFN+, respectively.

35 Figure 32 shows a comparison of single-modality adenovirus immunization with DNA + adjuvant prime/adenovirus boost immunization.

Figures 33A-B show the nucleotide sequence (SEQ ID NO: 38) of the open reading frame for the gag-IAPol fusion of Example 29.

Figures 34A-B show the protein sequence (SEQ ID NO:39) of the gag-IAPol fusion frame.

5

DETAILED DESCRIPTION OF THE INVENTION

A novel replication-defective, or "first generation," adenoviral vector suitable for use in gene therapy or nucleotide-based vaccine vectors is described. This vector is at least partially deleted in E1 and comprises a wildtype adenovirus *cis*-acting packaging region from about base pair 1 to between about base pair 342 (more preferably, 400) to about 458 (preferably, 1-450) and, preferably, 3511-3523 of a wild-type adenovirus sequence. It has been found that a vector of this description possesses enhanced growth characteristics, with approximately 5-10 fold greater amplification rates, and is more potent allowing lower doses of virus to be used to generate equivalent immunity. The vector, furthermore, generates a harvested recombinant adenovirus which shows greater cellular-mediated immune responses than replication-deficient vectors not comprising this region (basepairs 342-450). Adenoviral constructs derived from these vectors are, further, very stable genetically, particularly those comprising a transgene under the control of a hCMV promoter devoid of intron A. Viruses in accordance with this description were passaged continually and analyzed; see Example 12. Each virus analyzed maintained its correct genetic structure. Analysis was also carried out under propagation conditions similar to that performed in large scale production. Again, the vectors were found to possess enhanced genetic stability; see Figure 12. Following 21 passages, the viral DNA showed no evidence of rearrangement, and was highly reproducible from one production lot to the next. The outcome of all relevant tests indicate that the adenoviral vector is extremely well suited for large-scale production of recombinant, replication-deficient adenovirus, as shown herein with the data associated with Figure 28.

A preferred adenoviral vector in accordance with this description is a vector comprising basepairs 1-450, which is deleted in E3. This vector can accommodate up to approximately 7,500 base pairs of foreign DNA inserts (or exogenous genetic material). Another preferred vector is one retaining E3 which comprises basepairs 1-450. A preferred vector of this description is an E3+ vector comprising basepairs 1-450 and 3511-3523. This vector, when deleted of the region spanning basepairs 451-3510, can accommodate up to approximately, 4,850 base pairs of foreign DNA inserts

(or exogenous genetic material). The cloning capacities of the above vectors have been determined using 105% of the wildtype Ad5 sequence as the upper genome size limit.

Wildtype adenovirus serotype 5 is used as the basis for the specific basepair numbers provided throughout the specification. The wildtype adenovirus serotype 5 sequence is known and described in the art; *see*, Chroboczek *et al.*, 1992 *J. Virology* 186:280, which is hereby incorporated by reference. Accordingly, a particular embodiment of the instant invention is a vector based on the adenovirus serotype 5 sequence. One of skill in the art can readily identify the above regions in other adenovirus serotypes (e.g., serotypes 2, 4, 6, 12, 16, 17, 24, 31, 33, and 42), regions defined by basepairs corresponding to the above basepair positions given for adenovirus serotype 5. Accordingly, the instant invention encompasses all adenoviral vectors partially deleted in E1 comprising basepairs corresponding to 1-450 (particularly, 342-450) and, preferably, 3511-3523 of a wild-type adenovirus serotype 5 (Ad5) nucleic acid sequence. Particularly preferred embodiments of the instant invention are those derived from adenoviruses like Ad5 which are classified in subgroup C (e.g., Ad2).

Vectors in accordance with the instant invention are at least partially deleted in E1. Preferably the E1 region is completely deleted or inactivated. Most preferably, the region deleted of E1 is within basepairs 451-3510. It is to be noted that the extended 5' and 3' regions of the disclosed vectors are believed to effectively reduce the size of the E1 deletion of previous constructs without overlapping any part of the E1A/E1B gene present in the cell line used, i.e., the PER.C6[®] cell line transfected with base pairs 459-3510. Overlap of adenoviral sequences is avoided because of the possibility of recombination. One of ordinary skill in the art can certainly appreciate that the instant invention can, therefore, be modified if a different cell line transfected with a different segment of adenovirus DNA is utilized. For purposes of exemplification, a 5' region of base pairs 1 to up to 449 is more appropriate if a cell line is transfected with adenoviral sequence from base pairs 450-3510. This holds true as well in the consideration of segments 3' to the E1 deletion.

Preferred embodiments of the instant invention possess an intact E3 region (i.e., an E3 gene capable of encoding a functional E3). Alternate embodiments have a partially deleted E3, an inactivated E3 region, or a sequence completely deleted of E3. Applicants have found, in accordance with the instant invention, that virus comprising the E3 gene were able to amplify more rapidly compared with virus not comprising an E3 gene; see Figure 6 wherein a diagnostic CsCl band corresponding to the E3+ virus

tested (5,665 bp) was present in greater amount compared with the diagnostic band of 3,010 bp corresponding to the E3- virus. These results were obtained following a virus competition study involving mixing equal MOI ratio (1:1) of adenovectors both comprising the E3 gene and not comprising the E3 gene. This increased amplification capacity of the E3+ adenovectors was subsequently confirmed with growth studies; see Table 4A, wherein the E3+ virus exhibit amplification ratios of 470, 420 and 320 as compared with the 115 and 40-50 of the E3- constructs.

As stated above, vectors in accordance with the instant invention can accommodate up to approximately 4,850 base pairs of exogenous genetic material for an E3+ vector and approximately 7,500 base pairs for an E3- vector. Preferably, the insert brings the adenoviral vector as close as possible to a wild-type genomic size (e.g., for Ad5, 35,935 basepairs). It is well known that adenovirus amplifies best when they are close to their wild-type genomic size.

The genetic material can be inserted in an E1-parallel or an E1 anti-parallel orientation, as such is illustrated in Figure 7A, 7B, 7C and Figure 8A. Particularly preferred embodiments of the instant invention, have the insert in an E1-parallel orientation. Applicants have found, via competition experiments with plasmids containing transgenes in differing orientation (Figure 8A), that vector constructs with the foreign DNA insert in an E1-parallel orientation amplify better and actually out-compete E1-antiparallel-oriented transgenes. Viral DNA analysis of the mixtures at passage 3 and certainly at passage 6, showed a greater ratio of the virus carrying the transgene in the E1 parallel orientation as compared with the E1 anti-parallel version. By passage 10, the only viral species observed was the adenovector with the transgene in the E1 parallel orientation for both transgenes tested.

Adenoviral vectors in accordance with the instant invention are particularly well suited to effectuate expression of desired proteins, one example of which is an HIV protein, particularly an HIV full length gag protein. Exogenous genetic material encoding a protein of interest can exist in the form of an expression cassette. A gene expression cassette preferably comprises (a) a nucleic acid encoding a protein of interest; (b) a heterologous promoter operatively linked to the nucleic acid encoding the protein; and (c) a transcription terminator.

The transcriptional promoter is preferably recognized by an eukaryotic RNA polymerase. In a preferred embodiment, the promoter is a "strong" or "efficient" promoter. An example of a strong promoter is the immediate early human cytomegalovirus promoter (Chapman et al, 1991 *Nucl. Acids Res* 19:3979-3986, which is incorporated by reference), preferably without intronic sequences. Most preferred

for use within the instant adenoviral vector is a human CMV promoter without intronic sequences, like intron A. Applicants have found that intron A, a portion of the human cytomegalovirus promoter (hCMV), constitutes a region of instability for adenoviral vectors. CMV without intron A has been found to effectuate (Examples 1-3) comparable expression capabilities *in vitro* when driving HIV gag expression and, furthermore, behaved equivalently to intron A-containing constructs in Balb/c mice *in vivo* with respect to their antibody and T-cell responses at both dosages of plasmid DNA tested (20 µg and 200 µg). Those skilled in the art will appreciate that any of a number of other known promoters, such as the strong immunoglobulin, or other eukaryotic gene promoters may also be used, including the EF1 alpha promoter, the murine CMV promoter, Rous sarcoma virus (RSV) promoter, SV40 early/late promoters and the beta-actin promoter.

In preferred embodiments, the promoter may also comprise a regulatable sequence such as the Tet operator sequence. This would be extremely useful, for example, in cases where the gene products are effecting a result other than that desired and repression is sought.

Preferred transcription termination sequences present within the gene expression cassette are the bovine growth hormone terminator/polyadenylation signal (bGHpA) and the short synthetic polyA signal (SPA) of 50 nucleotides in length, defined as follows: AATAAAAGATCTTTATTTTCATTAGATCTGTGTGTTGGT-TTTTGTGTG (SEQ ID NO:26).

The combination of the CMV promoter (devoid of the intron A region) with the BGH terminator is particularly preferred although other promoter/terminator combinations in the context of FG adenovirus may also be used.

Other embodiments incorporate a leader or signal peptide into the transgene. A preferred leader is that from the tissue-specific plasminogen activator protein, tPA. Examples include but are not limited to the various tPA-gag, tPA-pol and tPA-nef adenovirus-based vaccines disclosed throughout this specification.

In view of the improved adenovirus vectors described herein, an essential portion of the present invention are adenoviral-based HIV vaccines comprising said adenovirus backbones which may be administered to a mammalian host, preferably a human host, in either a prophylactic or therapeutic setting. The HIV vaccines of the present invention, whether administered alone or in combination regimens with other viral- or non-viral-based DNA vaccines, should elicit potent and broad cellular immune responses against HIV that will either lessen the likelihood of persistent virus infection and/or lead to the establishment of a clinically significant lowered virus load

subject to HIV infection or in combination with HAART therapy, mitigate the effects of previously established HIV infection (antiviral immunotherapy(ARI)). While any HIV antigen (e.g., gag, pol, nef, gp160, gp41, gp120, tat, rev, etc.) may be utilized in the herein described recombinant adenoviral vectors, preferred embodiments include the codon optimized p55 gag antigen (herein exemplified as MRKAd5gag), pol and nef. Sequences based on different Clades of HIV-1 are suitable for use in the instant invention, most preferred of which are Clade B and Clade C. Particularly preferred embodiments are those sequences (especially, codon-optimized sequences) based on consensus Clade B sequences. Preferred versions of the MRKAd5pol and MRKAd5nef series of adenoviral vaccines will encode modified versions of pol or nef, as discussed herein. Preferred embodiments of the MRKAd5HIV-1 vectors carrying HIV envelope genes and modifications thereof comprise the HIV codon-optimized *env* sequences of PCT International Applications PCT/US97/02294 and PCT/US97/10517, published August 28, 1997 (WO 97/31115) and December 24, 1997, respectively; both documents of which are hereby incorporated by reference.

A most preferred aspect of the instant invention is the disclosed use of the adenoviral vector described above to effectuate expression of HIV gag. Sequences for many genes of many HIV strains are publicly available in GENBANK and primary, field isolates of HIV are available from the National Institute of Allergy and Infectious Diseases (NIAID) which has contracted with Quality Biological (Gaithersburg, MD) to make these strains available. Strains are also available from the World Health Organization (WHO), Geneva Switzerland. It is preferred that the gag gene be from an HIV-1 strain (CAM-1; Myers et al, eds. "Human Retroviruses and AIDS: 1995, IIA3-IIA19, which is hereby incorporated by reference). This gene closely resembles the consensus amino acid sequence for the clade B (North American/European) sequence. Therefore, it is within the purview of the skilled artisan to choose an appropriate nucleotide sequence which encodes a specific HIV gag antigen, or immunologically relevant portion thereof. As shown in Example 25, a clade B or clade C based p55 gag antigen will potentially be useful on a global scale. As noted herein, the transgene of choice for insertion in to a DNA or MRKAd-based adenoviral vector of the present invention is a codon optimized version of p55 gag. Such a MRKAd5gag adenoviral vector is documented in Example 11 and is at least referred to herein as MRKAd5HIV-1gag. Of course, additional versions are contemplated, including but not limited to modifications such as promoter (e.g., mCMV for hCMV) and/or pA-terminations signal (SPA for bGH) switching, as well as generating MRK Ad5 backbones with or without deletion of the Ad5 E3 gene.

The present invention also relates a series of MRKAd5pol-based adenoviral vaccines which are shown herein to generate cellular immune responses subsequent to administration in mice and non-human primate studies. Several of the MRKAd5pol series are exemplified herein. One such adenoviral vector is referred to as

5 MRKAd5hCMV-inact opt pol(E3+), which comprises the MRKAd5 backbone, the hCMV promoter (no intron A), an inactivated pol transgene, and contains the Ad5 E3 gene in the adenoviral backbone. A second exemplified pre-adenovirus plasmid and concomitant virus is referred to as MRKAd5hCMV-inact opt pol(E3-), which is identical to the former adenoviral vector except that the E3 is deleted. Both

10 constructions contain a codon optimized, inactivated version of HIV-1 Pol, wherein at least the entire coding region is disclosed herein as SEQ ID NO:3 and the expressed protein is shown as SEQ ID NO:4 (see also Figure 17A-C and Table 1, which show targeted deletion for inactivated pol. This and other preferred codon optimized versions of HIV Pol as disclosed herein are essentially as described in U.S.

15 Application Serial No. 09/745,221, filed December 21, 2000 and PCT International Application PCT/US00/34724, also filed December 21, 2000, both documents which are hereby incorporated by reference. As disclosed in the above-mentioned documents, the open reading frame for these codon-optimized HIV-1 Pol-based DNA vaccines are represented by codon optimized DNA molecules encoding codon

20 optimized HIV-1 Pol (e.g. SEQ ID NO:2), codon optimized HIV-1 Pol fused to an amino terminal localized leader sequence (e.g. SEQ ID NO:6), and especially preferable, and exemplified by the MRKAd5-Pol construct in e.g., Example 19, biologically inactivated pol ("inact opt Pol"; e.g., SEQ ID NO:4) which is devoid of significant PR, RT, RNase or IN activity associated with wild type Pol. In addition, a

25 construct related to SEQ ID NO:4 is contemplated which contains a leader peptide at the amino terminal region of the IA Pol protein. A specific construct is ligated within an appropriate DNA plasmid vector containing regulatory regions operatively linked to the respective HIV-1 Pol coding region, with or without a nucleotide sequence encoding a functional leader peptide. To this end, various HIV-1 Pol constructs

30 disclosed herein relate to open reading frames for cloning to the enhanced first generation Ad vectors of the present invention (such a series of MRKAd5pol adenoviral vaccine vectors), including but not limited to wild type Pol (comprising the DNA molecule encoding WT opt Pol, as set forth in SEQ ID NO:2), tPA-opt WTPol, (comprising the DNA molecule encoding tPA Pol, as set forth in SEQ ID NO:6), inact

35 opt Pol (comprising the DNA molecule encoding IA Pol, as set forth in SEQ ID NO:4), and tPA-inact opt Pol, (comprising the DNA molecule encoding tPA-inact opt

Pol, as set forth in SEQ ID NO:8). The pol-based versions of enhanced first generation adenovirus vaccines elicit CTL and Th cellular immune responses upon administration to the host, including primates and especially humans. As noted in the above, an effect of the cellular immune-directed vaccines of the present invention should be a lower transmission rate to previously uninfected individuals and/or reduction in the levels of the viral loads within an infected individual, so as to prolong the asymptomatic phase of HIV-1 infection.

The present invention further relates to a series of MRKAd5nef-based adenoviral vaccines which, similar to HIV gag and pol antigens, generate cellular immune responses subsequent to administration in mice and non-human primate studies. The MRKAd5nef series are exemplified herein by utilizing the improved MRK adenoviral backbone in combination with modified versions of HIV nef. These exemplified MRKAd5nef vectors are as follows: (1) MRKAd5hCMV-nef(G2A,LLAA) (E3+), which comprises the improved MRKAd5 backbone, a human CMV promoter an intact Ad5 E3 gene and a modified nef gene: (2) MRKAd5mCMV-nef(G2A,LLAA) (E3+), which is the same as (1) above but substituting a murine CMV promoter for a human CMV promoter; and (3) MRKAd5mCMV-tpanef(LLAA) (E3+), which is the same as (2) except that the nef transgene is tpanef(LLAA). Codon optimized versions of HIV-1 Nef and HIV-1 Nef modifications are essentially as described in U.S. Application Serial No. 09/738,782, filed December 15, 2000 and PCT International Application PCT/US00/34162, also filed December 15, 2000, both documents which are hereby incorporated by reference. Particular embodiments of codon optimized Nef and Nef modifications relate to a DNA molecule encoding HIV-1 Nef from the HIV-1 jfrrl isolate wherein the codons are optimized for expression in a mammalian system such as a human. The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:9, while the expressed open reading frame is disclosed herein as SEQ ID NO:10. Another embodiment of Nef-based coding regions for use in the adenoviral vectors of the present invention comprise a codon optimized DNA molecule encoding a protein containing the human plasminogen activator (tpa) leader peptide fused with the NH₂-terminus of the HIV-1 Nef polypeptide. The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:11, while the expressed open reading frame is disclosed herein as SEQ ID NO:12. Another modified Nef optimized coding region relates to a DNA molecule encoding optimized HIV-1 Nef wherein the open reading frame codes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175, herein

described as opt nef (G2A, LLAA). The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:13, while the expressed open reading frame is disclosed herein as SEQ ID NO:14. MRKAd5nef vectors (1) MRKAd5hCMV-nef(G2A,LLAA) (E3+) and (2) MRKAd5mCMV-nef(G2A,LLAA) (E3+) contain this
5 transgene. An additional embodiment relates to a DNA molecule encoding optimized HIV-1 Nef wherein the amino terminal myristylation site and dileucine motif have been deleted, as well as comprising a tPA leader peptide. This DNA molecule, opt tpanef (LLAA), comprises an open reading frame which encodes a Nef protein containing a tPA leader sequence fused to amino acid residue 6-216 of HIV-1 Nef
10 (jfr1), wherein Leu-174 and Leu-175 are substituted with Ala-174 and Ala-175, herein referred to as opt tpanef (LLAA) is disclosed herein as SEQ ID NO:15, while the expressed open reading frame is disclosed herein as SEQ ID NO:16. The MRKAd5nef vector "MRKAd5mCMV-tpanef(LLAA) (E3+)" contains this transgene.

Along with the improved MRKAd5gag adenovirus vaccine vector described
15 herein, generation of a MRKAd5pol and MRKAd5nef adenovirus vector provide for enhanced HIV vaccine capabilities. Namely, the generation of this trio of adenoviral vaccine vectors, all shown to generate effective cellular immune responses subsequent to host administration, provide for the ability to administer these vaccine candidates not only alone, but preferably as part of a divalent (i.e., gag and nef, gag and pol, or
20 pol and nef components) or a trivalent vaccine (i.e., gag, pol and nef components). Therefore, a preferred aspect of the present invention are vaccine formulations and associated methods of administration and concomitant generation of host cellular immune responses associated with formulating three separate series of MRKAd5-based adenoviral vector vaccines. Of course, this MRKAd5 vaccine series based on
25 distinct HIV antigens promotes expanded opportunities for formulation of a divalent or trivalent vaccine, or possibly administration of separate formulations of one or more monovalent or divalent formulations within a reasonable window of time. It is also within the scope of the present invention to embark on combined modality regimes which include multiple but distinct components from a specific antigen. An
30 example, but certainly not a limitation, would be separate MRKAd5pol vectors, with one vaccine vector expressing wild type Pol (SEQ ID NO:2) and another MRKAd5pol vector expressing inactivated Pol (SEQ ID NO:6). Another example might be separate MRKAd5nef vectors, with one vaccine vector expressing the tPA/LLAA version of Nef (SEQ ID NO:16) and another MRKAd5nef vector
35 expressing the G2A,LLAA modified version of Nef (SEQ ID NO:14). Therefore, the MRKAd5 adenoviral vectors of the present invention may be used in combination

with multiple, distinct HIV antigen classes. Each HIV antigen class is subject to sequence manipulation, thus providing for a multitude of potential vaccine combinations; and such combinations are within the scope of the present invention. The utilization of such combined modalities vaccine formulation and administration
5 increase the probability of eliciting an even more potent cellular immune response when compared to inoculation with a single modality regimen.

The present invention also relates to application of a mono-, dual-, or tri-modality administration regime of the MRKAd5gag, pol and nef adenoviral vaccine series in a prime/boost vaccination schedule. This prime/boost schedule may include
10 any reasonable combination of the MRKAd5gag, pol and nef adenoviral vaccine series disclosed herein. In addition, a prime/boost regime may also involve other viral and/or non-viral DNA vaccines. A preferable addition to an adenoviral vaccine vector regime includes but is not limited to plasmid DNA vaccines, especially DNA plasmid vaccines that contain at least one of the codon optimized gag, pol and nef
15 constructions, as disclosed herein.

Therefore, one aspect of this invention is the administration of the adenoviral vector containing the optimized gag gene in a prime/boost regiment in conjunction with a plasmid DNA encoding gag. To distinguish this plasmid from the adenoviral-containing shuttle plasmids used in the construction of an adenovirus vector, this
20 plasmid will be referred to as a "vaccine plasmid" or "DNA plasmid vaccine". Preferred vaccine plasmids for use in this administration protocol are disclosed in pending U.S. patent application 09/017,981, filed February 3, 1998 and WO98/34640, published August 13, 1998, both of which are hereby incorporated by reference. Briefly, the preferred vaccine plasmid is designated V1Jns-FLgag, which expresses
25 the same codon-optimized gag gene as the adenoviral vectors of this invention (see Figure 2 for the nucleotide sequence of the exemplified optimized codon version of full length p55 gag). The vaccine plasmid backbone, designated V1Jns contains the CMV immediate-early (IE) promoter and intron A, a bovine growth hormone-derived polyadenylation and transcription termination sequence as the gene expression
30 regulatory elements, and a minimal pUC backbone; see Montgomery *et al.*, 1993, *DNA Cell Biol.* 12:777-783. The pUC sequence permits high levels of plasmid production in *E. coli* and has a neomycin resistance gene in place of an ampicillin resistance gene to provide selected growth in the presence of kanamycin. Alternatively, a vaccine plasmid which has the CMV promoter deleted of intron A can
35 be used. Those of skill in the art will recognize that alternative vaccine plasmid

vectors may be easily substituted for these specific constructs, and this invention specifically envisions use of such alternative plasmid DNA vaccine vectors.

Another aspect of the present invention is a prime/boost regimen which includes a vaccine plasmid which encodes an HIV pol antigen, preferably a codon
5 optimized form of pol and also preferably a vaccine plasmid which comprises a nucleotide sequence which encodes a Pol antigen selected from the group of Pol antigens as shown in SEQ ID NOs: 2, 4, 6 and 8. The variety of potential DNA plasmid vaccines which encode various biologically active forms of HIV-1 Pol, wherein administration, intracellular delivery and expression of the HIV-1 Pol gene of
10 interest elicits a host CTL and Th response. The preferred synthetic DNA molecules of the present invention encode codon optimized wild type Pol (without Pro activity) and various codon optimized inactivated HIV-1 Pol proteins. The HIV-1 *pol* open reading disclosed herein are especially preferred for pharmaceutical uses, especially for human administration as delivered via a recombinant adenoviral vaccine,
15 especially an enhanced first generation recombinant adenoviral vaccine as described herein. Several embodiments of this portion of the invention are provided in detail below, namely DNA molecules which comprise a HIV-1 pol open reading frame, whether encoding full length pol or a modification or fusion as described herein, wherein the codon usage has been optimized for expression in a mammal, especially a
20 human. Again, these DNA sequences are positioned appropriately within a recombinant adenoviral vector, such as the exemplified recombinant adenoviral vector described herein, so as to promote expression of the respective HIV-1 Pol gene of interest, and subsequent to administration, elicit a host CTL and Th response. Again, these preferred, but in no way limiting, pol genes are as disclosed herein and
25 essentially as described in U.S. Application Serial No. 09/745,221, filed December 21, 2000 and PCT International Application PCT/US00/34724, also filed December 21, 2000, both documents which are hereby incorporated by reference.

A third series of vaccine plasmids which are useful in a combined modality and/or prime/boost regimen are vaccine plasmids which encode an HIV nef antigen or
30 biologically and/or immunologically relevant modification thereof. As noted elsewhere, preferred vaccine plasmids contain a codon optimized form of nef and also preferably comprise a nucleotide sequence which encodes a Nef antigen selected from the group of Nef antigens as shown in SEQ ID NOs: 10, 12, 14 and 16. These preferred nef coding regions are disclosed herein, as well as being described in U.S.
35 Application Serial No. 09/738,782, filed December 15, 2000 and PCT International

Application PCT/US00/34162, also filed December 15, 2000, both documents which are hereby incorporated by reference.

Therefore, the adenoviral vaccines and plasmid DNA vaccines of this invention may be administered alone, or may be part of a prime and boost administration regimen. A mixed modality priming and booster inoculation scheme will result in an enhanced immune response, particularly if pre-existing anti-vector immune responses are present. This one aspect of this invention is a method of priming a subject with the plasmid vaccine by administering the plasmid vaccine at least one time, allowing a predetermined length of time to pass, and then boosting by administering the adenoviral vaccine. Multiple primings typically, 1-4, are usually employed, although more may be used. The length of time between priming and boost may typically vary from about four months to a year, but other time frames may be used. In experiments with rhesus monkeys, the animals were primed four times with plasmid vaccines, then were boosted 4 months later with the adenoviral vaccine. Their cellular immune response was notably higher than that of animals which had only received adenoviral vaccine. The use of a priming regimen may be particularly preferred in situations where a person has a pre-existing anti-adenovirus immune response.

Furthermore and in the alternative, multiple HIV-1 viral antigens, such as the MRKAd5 adenoviral vaccines disclosed herein, may be ligated into a proper shuttle plasmid for generation of a pre-adenoviral plasmid comprising multiple open reading frames. For example a trivalent vector may comprise a gag-pol-nef fusion, in either a E3(-) or E3(+) background, preferably a E3 deleted backbone, or possibly a "2+1" divalent vaccine, such as a gag-pol fusion (i.e., codon optimized p55 gag and inactivated optimized pol; Example 29 and Table 25) within the same MRKAd5 backbone, with each open reading frame being operatively linked to a distinct promoter and transcription termination sequence. Alternatively, the two open reading frames may be operatively linked to a single promoter, with the open reading frames operatively linked by an internal ribosome entry sequence (IRES), as disclosed in International Publication No. WO 95/24485, which is hereby incorporated by reference. Figure 9 shows that the use of multiple promoters and termination sequences provide for similar growth properties, while Figure 28 shows that these MRKAd5gag-based vectors are also stable at least through passage 21. In the absence of the use of IRES-based technology, it is preferred that a distinct promoter be used to support each respective open reading frame, so as to best preserve vector stability. As examples, and certainly not as limitations, potential multiple transgene vaccines may

include a three transgene vector such as hCMV-gagpol-bGHpA + mCMV-nef-SPA in an E3 deleted backbone or hCMV-gagpol-bGHpA + mCMV-nef-SPA(E3+).

Potential "2+1" divalent vaccines of the present invention might be a hCMV-gag-bGHpA + mCMV-nef-SPA in an E3+ backbone (vector #1) in combination with
5 hCMV-pol-bGHpA in an E3+ backbone (vector #2), with all transgenes in the E1 parallel orientation. Fusion constructs other than the gag-pol fusion described above are also suitable for use in various divalent vaccine strategies and can be composed of any two HIV antigens fused to one another (*e.g.*, nef-pol and gag-nef). These adenoviral compositions are, as above, preferably delivered along with an adenoviral
10 composition comprising an additional HIV antigen in order to diversify the immune response generated upon administration. Therefore, a multivalent vaccine delivered in a single, or possible second, adenoviral vector is certainly contemplated as part of the present invention. Again, this mode of administration is another example of whereby an efficacious adenovirus-based HIV-1 vaccine may be administered via a
15 combined modality regime. It is important to note, however, that in terms of deciding on an insert for the disclosed adenoviral vectors, due consideration must be dedicated to the effective packaging limitations of the adenovirus vehicle. Adenovirus has been shown to exhibit an upper cloning capacity limit of approximately 105% of the wildtype Ad5 sequence.

20 Regardless of the gene chosen for expression, it is preferred that the sequence be "optimized" for expression in a human cellular environment. A "triplet" codon of four possible nucleotide bases can exist in 64 variant forms. That these forms provide the message for only 20 different amino acids (as well as transcription initiation and termination) means that some amino acids can be coded for by more than one codon.
25 Indeed, some amino acids have as many as six "redundant", alternative codons while some others have a single, required codon. For reasons not completely understood, alternative codons are not at all uniformly present in the endogenous DNA of differing types of cells and there appears to exist variable natural hierarchy or "preference" for certain codons in certain types of cells. As one example, the amino
30 acid leucine is specified by any of six DNA codons including CTA, CTC, CTG, CTT, TTA, and TTG (which correspond, respectively, to the mRNA codons, CUA, CUC, CUG, CUU, UUA and UUG). Exhaustive analysis of genome codon frequencies for microorganisms has revealed endogenous DNA of *E. coli* most commonly contains the CTG leucine-specifying codon, while the DNA of yeasts and slime molds most
35 commonly includes a TTA leucine-specifying codon. In view of this hierarchy, it is generally held that the likelihood of obtaining high levels of expression of a leucine-

rich polypeptide by an *E. coli* host will depend to some extent on the frequency of codon use. For example, a gene rich in TTA codons will in all probability be poorly expressed in *E. coli*, whereas a CTG rich gene will probably highly express the polypeptide. Similarly, when yeast cells are the projected transformation host cells for expression of a leucine-rich polypeptide, a preferred codon for use in an inserted DNA would be TTA.

The implications of codon preference phenomena on recombinant DNA techniques are manifest, and the phenomenon may serve to explain many prior failures to achieve high expression levels of exogenous genes in successfully transformed host organisms--a less "preferred" codon may be repeatedly present in the inserted gene and the host cell machinery for expression may not operate as efficiently. This phenomenon suggests that synthetic genes which have been designed to include a projected host cell's preferred codons provide a preferred form of foreign genetic material for practice of recombinant DNA techniques. Thus, one aspect of this invention is an adenovirus vector or adenovirus vector in some combination with a vaccine plasmid where both specifically include a gene which is codon optimized for expression in a human cellular environment. As noted herein, a preferred gene for use in the instant invention is a codon-optimized HIV gene and, particularly, HIV gag, pol or nef.

Adenoviral vectors in accordance with the instant invention can be constructed using known techniques, such as those reviewed in Hitt et al, 1997 "Human Adenovirus Vectors for Gene Transfer into Mammalian Cells" *Advances in Pharmacology* 40:137-206, which is hereby incorporated by reference.

In constructing the adenoviral vectors of this invention, it is often convenient to insert them into a plasmid or shuttle vector. These techniques are known and described in Hitt et al., *supra*. This invention specifically includes both the adenovirus and the adenovirus when inserted into a shuttle plasmid.

Preferred shuttle vectors contain an adenoviral portion and a plasmid portion. The adenoviral portion is essentially the same as the adenovirus vector discussed *supra*, containing adenoviral sequences (with non-functional or deleted E1 and E3 regions) and the gene expression cassette, flanked by convenient restriction sites. The plasmid portion of the shuttle vector often contains an antibiotic resistance marker under transcriptional control of a prokaryotic promoter so that expression of the antibiotic does not occur in eukaryotic cells. Ampicillin resistance genes, neomycin resistance genes and other pharmaceutically acceptable antibiotic resistance markers may be used. To aid in the high level production of the polynucleotide by

fermentation in prokaryotic organisms, it is advantageous for the shuttle vector to contain a prokaryotic origin of replication and be of high copy number. A number of commercially available prokaryotic cloning vectors provide these benefits. It is desirable to remove non-essential DNA sequences. It is also desirable that the vectors not be able to replicate in eukaryotic cells. This minimizes the risk of integration of polynucleotide vaccine sequences into the recipients' genome. Tissue-specific promoters or enhancers may be used whenever it is desirable to limit expression of the polynucleotide to a particular tissue type.

In one embodiment of this invention, the pre-plasmids (e.g., pMRKAd5pol, pMRKAd5nef and pMRKAd5gag) were generated by homologous recombination using the MRKHVE3 (and MRKHVO for the E3- version) backbones and the appropriate shuttle vector, as shown for pMRKAd5pol in Figure 22 and for pMRKAd5nef in Figure 23. The plasmid in linear form is capable of replication after entering the PER.C6[®] cells and virus is produced. The infected cells and media were harvested after viral replication was complete.

Viral vectors can be propagated in various E1 complementing cell lines, including the known cell lines 293 and PER.C6[®]. Both these cell lines express the adenoviral E1 gene product. PER.C6[®] is described in WO 97/00326 (published January 3, 1997) and issued U.S. Patent No. 6,033,908, both of which are hereby incorporated by reference. It is a primary human retinoblast cell line transduced with an E1 gene segment that complements the production of replication deficient (FG) adenovirus, but is designed to prevent generation of replication competent adenovirus by homologous recombination. Cells of particular interest have been stably transformed with a transgene that encodes the AD5E1A and E1B gene, like PER.C6[®], from 459 bp to 3510 bp inclusive. 293 cells are described in Graham et al., 1977 *J. Gen. Virol* 36:59-72, which is hereby incorporated by reference. As stated above, consideration must be given to the adenoviral sequences present in the complementing cell line used. It is important that the sequences not overlap with that present in the vector if the possibility of recombination is to be minimized.

It has been found that vectors generated in accordance with the above description are more effective in inducing an immune response and, thus, constitute very promising vaccine candidates. More particularly, it has been found that first generation adenoviral vectors in accordance with the above description carrying a codon-optimized HIV gag gene, regulated with a strong heterologous promoter can be used as human anti-HIV vaccines, and are capable of inducing immune responses.

Standard techniques of molecular biology for preparing and purifying DNA constructs enable the preparation of the DNA immunogens of this invention.

A vaccine composition comprising an adenoviral vector in accordance with the instant invention may contain physiologically acceptable components, such as
5 buffer, normal saline or phosphate buffered saline, sucrose, other salts and polysorbate. One preferred formulation has: 2.5-10 mM TRIS buffer, preferably about 5 mM TRIS buffer; 25-100 mM NaCl, preferably about 75 mM NaCl; 2.5-10% sucrose, preferably about 5% sucrose; 0.01 -2 mM $MgCl_2$; and 0.001%-0.01% polysorbate 80 (plant derived). The pH should range from about 7.0-9.0, preferably
10 about 8.0. One skilled in the art will appreciate that other conventional vaccine excipients may also be used it make the formulation. The preferred formulation contains 5mM TRIS, 75 mM NaCl, 5% sucrose, 1mM $MgCl_2$, 0.005% polysorbate 80 at pH 8.0 This has a pH and divalent cation composition which is near the optimum for Ad5 stability and minimizes the potential for adsorption of virus to a glass surface.
15 It does not cause tissue irritation upon intramuscular injection. It is preferably frozen until use.

The amount of adenoviral particles in the vaccine composition to be introduced into a vaccine recipient will depend on the strength of the transcriptional and translational promoters used and on the immunogenicity of the expressed gene
20 product. In general, an immunologically or prophylactically effective dose of 1×10^7 to 1×10^{12} particles and preferably about 1×10^{10} to 1×10^{11} particles is administered directly into muscle tissue. Subcutaneous injection, intradermal introduction, impression through the skin, and other modes of administration such as intraperitoneal, intravenous, or inhalation delivery are also contemplated. It is also
25 contemplated that booster vaccinations are to be provided. Following vaccination with HIV adenoviral vector, boosting with a subsequent HIV adenoviral vector and/or plasmid may be desirable. Parenteral administration, such as intravenous, intramuscular, subcutaneous or other means of administration of interleukin-12 protein, concurrently with or subsequent to parenteral introduction of the vaccine
30 compositions of this invention is also advantageous.

The adenoviral vector and/or vaccine plasmids of this invention polynucleotide may be unassociated with any proteins, adjuvants or other agents which impact on the recipients' immune system. In this case, it is desirable for the vector to be in a physiologically acceptable solution, such as, but not limited to, sterile
35 saline or sterile buffered saline. Alternatively, the vector may be associated with an adjuvant known in the art to boost immune responses (i.e., a "biologically effective"

adjuvant), such as a protein or other carrier. Vaccine plasmids of this invention may, for instance, be delivered in saline (e.g., PBS) with or without an adjuvant. Preferred adjuvants are Alum or CRL1005 Block Copolymer. Agents which assist in the cellular uptake of DNA, such as, but not limited to, calcium ions, may also be used to
5 advantage. These agents are generally referred to herein as transfection facilitating reagents and pharmaceutically acceptable carriers. Techniques for coating microprojectiles coated with polynucleotide are known in the art and are also useful in connection with this invention.

This invention also includes a prime and boost regimen wherein a first
10 adenoviral vector is administered, then a booster dose is given. The booster dose may be repeated at selected time intervals. Alternatively, a preferred inoculation scheme comprises priming with a first adenovirus serotype and then boosting with a second adenovirus serotype. More preferably, the inoculation scheme comprises priming with a first adenovirus serotype and then boosting with a second adenovirus serotype,
15 wherein the first and second adenovirus serotypes are classified within separate subgroups of adenoviruses. The above prime/boost schemes are particularly preferred in those situations where a preexisting immunity is identified to the adenoviral vector of choice. In this type of scheme, the individual or population of individuals is primed with an adenovirus of a serotype other than that to which the preexisting
20 immunity is identified. This enables the first adenovirus to effectuate sufficient expression of the transgene while evading existing immunity to the second adenovirus (the boosting adenovirus) and, further, allows for the subsequent delivery of the transgene via the boosting adenovirus to be more effective. Adenovirus serotype 5 is one example of a virus to which such a scheme might be desirable. In accordance
25 with this invention, therefore, one might decide to prime with a non-group C adenovirus (e.g., Ad12, a group A adenovirus, Ad24, a group D adenovirus, or Ad35, a group B adenovirus) to evade anti-Ad5 immunity and then boost with Ad5, a group C adenovirus. Another preferred embodiment involves administration of a different adenovirus (including non-human adenovirus) vaccine followed by administration of
30 the adenoviral vaccines disclosed. In the alternative, a viral antigen of interest can be first delivered via a viral vaccine other than an adenovirus-based vaccine, and then followed with the adenoviral vaccine disclosed. Alternative viral vaccines include but are not limited to pox virus and venezuelan equine encephalitis virus.

A large body of human and animal data supports the importance of cellular
35 immune responses, especially CTL in controlling (or eliminating) HIV infection. In humans, very high levels of CTL develop following primary infection and correlate

with the control of viremia. Several small groups of individuals have been described who are repeatedly exposed to HIV by remain uninfected; CTL has been noted in several of these cohorts. In the SIV model of HIV infection, CTL similarly develops following primary infection, and it has been demonstrated that addition of anti-CD8 monoclonal antibody abrogated this control of infection and leads to disease progression. This invention uses adenoviral vaccines alone or in combination with plasmid vaccines to induce CTL.

The following non-limiting Examples are presented to better illustrate the invention.

EXAMPLE 1

Removal of the Intron A Portion of the hCMV Promoter

GMP grade pVII_{ns}HIVgag was used as the starting material to amplify the hCMV promoter. PVI_{ns}HIVgag is a plasmid comprising the CMV immediate-early (IE) promoter and intron A, a full-length codon-optimized HIV gag gene, a bovine growth hormone-derived polyadenylation and transcriptional termination sequence, and a minimal pUC backbone; see Montgomery *et al.*, *supra* for a description of the plasmid backbone. The amplification was performed with primers suitably positioned to flank the hCMV promoter. A 5' primer was placed upstream of the *MscI* site of the hCMV promoter and a 3' primer (designed to contain the *BglII* recognition sequence) was placed 3' of the hCMV promoter. The resulting PCR product (using high fidelity *Taq* polymerase) which encompassed the entire hCMV promoter (minus intron A) was cloned into TOPO PCR blunt vector and then removed by double digestion with *MscI* and *BglII*. This fragment was then cloned back into the original GMP grade pVI_{ns}HIVgag plasmid from which the original promoter, intron A, and the gag gene were removed following *MscI* and *BglII* digestion. This ligation reaction resulted in the construction of a hCMV promoter (minus intron A) + bGHpA expression cassette within the original pVI_{ns}HIVgag vector backbone. This vector is designated pVII_{ns}CMV(no intron).

The FLgag gene was excised from pVI_{ns}HIVgag using *BglII* digestion and the 1,526 bp gene was gel purified and cloned into pVI_{ns}CMV(no intron) at the *BglII* site. Colonies were screened using *SmaI* restriction enzymes to identify clones that carried the FLgag gene in the correct orientation. This plasmid, designated pVI_{ns}CMV(no intron)-FLgag-bGHpA, was fully sequenced to confirm sequence integrity.

Two additional transgenes were also constructed. The plasmid, pV1JnsCMV(no intron)-FLgag-SPA, is identical to pV1JnsCMV(no intron)-FLgag-bGHpA except that the bovine growth hormone polyadenylation signal has been replaced with a short synthetic polyA signal (SPA) of 50 nucleotides in length. The sequence of the SPA is as shown, with the essential components (poly(A) site, (GT)_n, and (T)_n; respectively) underlined:

AATAAAAGATCTTTATTTTCATTAGATCTGTGTG TTGGTTTTTTGTGTG
(SEQ ID NO:18).

The plasmid, pV1Jns-mCMV-FLgag-bGHpA, is identical to the pV1JnsCMV(no intron)-FLgag-bGHpA except that the hCMV promoter has been removed and replaced with the murine CMV (mCMV) promoter.

Figure 3 diagrammatically shows the new transgene constructs in comparison with the original transgene.

EXAMPLE 2

Gag Expression Assay for Modified Gag Transgenes

Gag Elisa was performed on culture supernatants obtained from transient tissue culture transfection experiments in which the two new hCMV-containing plasmid constructs, pV1JnsCMV(no intron)-FLgag-bGHpA and pV1JnsCMV(no intron)-FLgag-SPA, both devoid of intron A, were compared to pV1JnsHIVgag which, as noted above possesses the intron A as part of the hCMV promoter. Table 2 below shows the *in vitro* gag expression data of the new gag plasmids compared with the GMP grade original plasmid. The results displayed in Table 2 show that both of the new hCMV gag plasmid constructs have expression capacities comparable to the original plasmid construct which contains the intron A portion of the hCMV promoter.

Table 2: *In vitro* DNA transfection of original and new plasmid HIV-1 gag constructs.

Plasmid	$\mu\text{g gag}/10\text{e}6 \text{ COS cells}/5\mu\text{g DNA}/48 \text{ hr}$
HIVFL-gagPR9901 ^a	10.8
PV1Jns-hCMV-FLgag-bGHpA ^b	16.6
pV1Jns-hCMV-FLgag-SPA ^{b,c}	12.0

^a GMP grade pV1Jns-hCMVintronA-FLgag-bGHpA.

5 ^b New plasmid constructions that have the intron A portion removed from the hCMV promoter.

^c In this construct the bGH terminator has been replaced with the short synthetic polyadenylation signal (SPA)

10

EXAMPLE 3

Rodent (Balb/c) Study for Modified gag Transgenes

A rodent study was performed on the two new plasmid constructs described above – pV1JnsCMV(no intron)-FLgag-bGHpA and pV1JnsCMV(no intron)-FLgag-SPA - in order to compare them with the construct described above possessing the intron A portion of the CMV promoter, pV1JnsHIVgag. Gag antibody and Elispot responses (described in PCT International Application No. 15 PCT/US00/18332 (WO 01/02607) filed July 3, 2000, claiming priority to U.S. Provisional Application Serial No. 60/142,631, filed July 6, 1999 and U.S. Application Serial No. 60/148,981, filed August 13, 1999, all three applications which 20 are hereby incorporated by reference) were measured. The results displayed in Table 3 below, show that the new plasmid constructs behaved equivalently to the original construct in Balb/c mice with respect to their antibody and T-cell responses at both dosages of plasmid DNA tested, 20 μg and 200 μg .

EXAMPLE 4

Table 3: HIV191: Immunogenicity of V1Jns-gag under different promoter and termination control elements.

DNA ^a Promoter/terminator	Dose, ug ^b	Anti-p24 Titers (3 Wk PD1) ^c			SFC/10 ⁶ Cells (4 Wk PD1) ^d		
		GMT	+SE	-SE	Media	gag197-205	p24
HIVFL-gagPR9901 (GMP grade)	200	12800	4652	3412	2(2)	129(19)	30(11)
	20	5572	1574	1227	0	56(9)	25(6)
pV1Jns-hCMV- FL-gag-bGHPA	200	11143	2831	2257	0	98(5)	12(6)
	20	7352	2808	2032	0	73(9)	11(6)
pV1Jns-hCMV- FL-gag-SPA	200	16890	5815	4326	1(1)	94(4)	26(7)
	20	5971	5361	2825	0	85(17)	38(10)
Naïve	0	123	50	36	0	0	0

^aIn PBS^bi.m. Injections into both quads, 50 µL per quad^cn=10; GMT, geometric mean titer; SE, standard. error^dn=5, pooled spleens; mean of triplicate wells and standard. deviation. in parentheses;

Construction of the Modified Shuttle Vector -"MRKpdeIE1 Shuttle"

- The modifications to the original Ad5 shuttle vector (pdeIE1sp1A; a vector comprising Ad5 sequences from basepairs 1-341 and 3524-5798, with a multiple cloning region between nucleotides 341 and 3524 of Ad5, included the following three manipulations carried out in sequential cloning steps as follows:
- (1) The left ITR region was extended to include the *Pac1* site at the junction between the vector backbone and the adenovirus left ITR sequences. This allow for easier manipulations using the bacterial homologous recombination system.
 - (2) The packaging region was extended to include sequences of the wild-type (WT) adenovirus from 342 bp to 450 bp inclusive.
 - (3) The area downstream of pIX was extended 13 nucleotides (i.e., nucleotides 3511-3523 inclusive).

These modifications (Figure 4) effectively reduced the size of the E1 deletion without overlapping with any part of the E1A/E1B gene present in the transformed PER.C6[®] cell line. All manipulations were performed by modifying the Ad shuttle vector pdeIE1sp1A.

Once the modifications were made to the shuttle vector, the changes were incorporated into the original Ad5 adenovector backbones (pAdHVO and pAdHVE3) by bacterial homologous recombination using *E. coli* BJ5183 chemically competent cells.

EXAMPLE 5

Construction of Modified Adenovector Backbones (E3+ and E3-)

The original adenovectors pAdHVO (comprising all Ad5 sequences except those nucleotides encompassing the E1 and E3 regions) and pAdHVE3 (comprising all Ad5 sequences except those nucleotides encompassing the E1 region), were each reconstructed so that they contained the modifications to the E1 region. This was accomplished by digesting the newly modified shuttle vector (MRKpdeIE1 shuttle) with *PacI* and *BstZ1101* and isolating the 2,734 bp fragment which corresponds to the adenovirus sequence. This fragment was co-transformed with DNA from either *ClaI* linearized pAdHVO (E3- adenovector) or *ClaI* linearized pAdHVE3 (E3+adenovector) into *E. coli* BJ5183 competent cells. At least two colonies from each transformation were selected and grown in Terrific™ broth for 6-8 hours until turbidity was reached. DNA was extracted from each cell pellet and then transformed into *E. coli* XL1 competent cells. One colony from each transformation was selected and grown for plasmid DNA purification. The plasmid was analyzed by restriction digestions to identify correct clones. The modified adenovectors were designated MRKpAdHVO (E3- plasmid) and MRKpAdHVE3 (E3+ plasmid). Virus from these new adenovectors (MRKHVO and MRKHVE3, respectively) as well as the old version of the adenovectors were generated in the PER.C6® cell lines to accommodate the following series of viral competition experiments. In addition, the multiple cloning site of the original shuttle vector contained *ClaI*, *BamHI*, *Xho I*, *EcoRV*, *HindIII*, *Sal I*, and *Bgl II* sites. This MCS was replaced with a new MCS containing *Not I*, *Cla I*, *EcoRV* and *Asc I* sites. This new MCS has been transferred to the MRKpAdHVO and MRKpAdHVE3 pre-plasmids along with the modification made to the packaging region and pIX gene.

EXAMPLE 6

Analysis of the Effect of the Packaging Signal Extension

To study the effects of the modifications made to the E1 deletion region, the viruses obtained from the original backbone (pAdHVE3) and the new backbone (MRKpAdHVE3) were mixed together in equal MOI ratios (1:1 and 5:5) and passaged through several rounds; see Figure 5, Expt.#1. Both of the viruses in the experiment contained the E3 gene intact and did not contain a transgene. The only difference between the two viruses was within the region of the E1 deletion. Following the coinfection of the viruses at P1 (passage 1), the mixtures were propagated through an additional 4 passages at which time the cells were harvested

and the virus extracted and purified by CsCl banding. The viral DNA was extracted and digested with *Hind*III and the digestion products were then radioactively labeled. For the controls, the respective pre-plasmids (pAdHVE3 ("OLD E3+"); MRKpAdHVE3 ("NEW E3+")) were also digested with *Hind*III (and *Pac*I to remove the vector backbone) and subsequently labeled with [³³P]dATP. The radioactively labeled digestion products were subjected to gel electrophoresis and the gel was dried down onto Whatman paper before being exposed to autoradiographic film. Figure 6 clearly shows that the new adenovirus which has the addition made to the packaging signal region has a growth advantage compared with the original adenovirus. In the experiments performed (at either ratio tested), only the digestion bands pertaining to the newly modified virus were present. The diagnostic band of size 3,206 (from the new virus) was clearly present. However, there was no evidence of the diagnostic band of size 2,737 bp expected from the original virus.

EXAMPLE 7

Analysis of the Effect of the E3 Gene

The second set of the virus competition study involved mixing equal MOI ratio (1:1) of the newly modified viruses, that obtained from MRKpAdHVO and MRKpAdHVE3 (Figure 5, Expt. #2). In this set, both viruses had the new modifications made to the E1 deletion. The first virus (that from MRKpAdHVO) does not contain an E3 gene. The second virus (that from MRKpAdHVE3) does contain the E3 gene. Neither of the viruses contain a transgene. Following co-infection of the viruses, the mixtures were propagated through an additional 4 passages at which time the cells were harvested and the total virus extracted and purified by CsCl banding. The viral DNA was extracted and digested with *Hind*III and the digestion products were then radioactively labeled. For the controls, the respective pre-plasmids MRKpAdHVO ("NEW E3-"); MRKpAdHVE3 ("NEW E3+") were also digested with *Hind*III (and *Pac*I to remove the vector backbone) and then labeled with [³³P]dATP. The radioactively labeled digestion products were subjected to gel electrophoresis and the gel was dried down onto Whatman paper before being exposed to autoradiographic film. Figure 6 shows the results of the viral DNA analysis of the E3+ virus and E3- virus mixing experiment. The diagnostic band corresponding to the E3+ virus (5,665 bp) was present in greater amount compared with the diagnostic band of 3,010 bp corresponding to the E3- virus. This indicates that the virus that contains the E3 gene is able to amplify more rapidly

compared with the virus that does not contain an E3 gene. This increased amplification capacity has been confirmed by growth studies; see Table 4 below.

EXAMPLE 8

5 Construction of the new shuttle vector containing modified gag transgene –
 “MRKpdelE1-CMV(no intron)-FLgag-bGHpA”

 The modified plasmid pV1JnsCMV(no intron)-FLgag-bGHpA was digested with *MscI* overnight and then digested with *SfiI* for 2 hours at 50°C. The DNA was then treated with Mungbean nuclease for 30 mins at 30°C. The DNA mixture was
10 desalted using the Qiaex II kit and then Klenow treated for 30 mins at 37°C to fully blunt the ends of the transgene fragment. The 2,559 bp transgene fragment was then gel purified. The modified shuttle vector (MRKpdelE1 shuttle) was linearized by digestion with *EcoRV*, treated with calf intestinal phosphatase and the resulting 6,479 bp fragment was then gel purified. The two purified fragments were then ligated
15 together and several dozen clones were screened to check for insertion of the transgene within the shuttle vector. Diagnostic restriction digestion was performed to identify those clones carrying the transgene in the E1 parallel and E1 anti-parallel orientation. This strategy was followed to clone in the other gag transgenes in the MRKpdelE1 shuttle vector.

20

EXAMPLE 9

Construction of the MRK FG Adenovectors

 The shuttle vector containing the HIV-1 gag transgene in the E1 parallel orientation, MRKpdelE1-CMV(no intron)-FLgag-bGHpA, was digested with *PacI*.
25 The reaction mixture was digested with *BsfZ171*. The 5,291 bp fragment was purified by gel extraction. The MRKpAdHVE3 plasmid was digested with *ClaI* overnight at 37°C and gel purified. About 100 ng of the 5,290 bp shuttle +transgene fragment and ~100 ng of linearized MRKpAdHVE3 DNA were co-transformed into *E. coli* BJ5183 chemically competent cells. Several clones were selected and grown in 2 ml
30 Terrific™ broth for 6-8 hours, until turbidity was reached. The total DNA from the cell pellet was purified using Qiagen alkaline lysis and phenol chloroform method. The DNA was precipitated with isopropanol and resuspended in 20 µl dH₂O. A 2 µl aliquot of this DNA was transformed into *E. coli* XL-1 competent cells. A single colony from each separate transformation was selected and grown overnight in 3 ml
35 LB +100 µg/ml ampicillin. The DNA was isolated using Qiagen columns. A positive clone was identified by digestion with the restriction enzyme *BstEII* which cleaves

within the gag gene as well as the plasmid backbone. The pre-plasmid clone is designated MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA and is 37,498 bp in size. This strategy was followed to generate E3- and E3+ versions of each of the other gag transgene constructions in both E1 parallel and E1 anti-parallel versions. Figures 7A, 7B and 7C show the various combinations of adenovectors constructed.

EXAMPLE 10

Plasmid Competition Studies

A series of plasmid competition studies was carried out. Briefly, the screening of the various combinations of new constructs was performed by mixing equal amounts of each of two competing plasmids. In the experiment shown in Figure 8A, plasmids containing the same transgene but in different orientations were mixed together to create a "competition" between the two plasmids. The aim was to look at the effects of transgene orientation. In the experiment shown in Figure 8B, plasmids containing different polyadenylation signals (but in the same orientation) were mixed together in equal amounts. The aim was to assess effects of polyA signals. Following the initial transfection, the virus was passaged through ten rounds and the viral DNA analyzed by radioactive restriction analysis.

Analysis of the viral species from the plasmid mixing experiment (Figure 8A) showed that adenovectors which had the transgene inserted in the E1 parallel orientation amplified better and were able to out-compete the adenovirus which had the transgene inserted in the E1 anti-parallel orientation. Viral DNA analysis of the mixtures at passage 3 and certainly at passage 6, showed a greater ratio of the virus carrying the transgene in the E1 parallel orientation compared with the E1 antiparallel version. By passage 10, the only viral species observed was the adenovector with the transgene in the E1 parallel orientation for both transgenes tested (hCMV(no intron)-FLgag-bGHpA and hCMV(no intron)-FLgag-SPA).

Analysis of the viral species from the plasmid mixing experiment #2 (Figure 8B) at passages 3 and 6 showed that the polyadenylation signals tested (bGHpA and SPA) did not have an effect on the growth of the virus. Even at passage 10 the two viral species in the mixture were still present in equal amounts.

EXAMPLE 11

Virus generation of an enhanced adenoviral construct – “MRK Ad5 HIV-1 gag”

The results obtained from the competition study allowed us to make the following conclusions: (1) The packaging signal extension is beneficial; (2) Presence
5 of E3 does enhance viral growth; (3) E1 parallel orientation is recommended; and (4) PolyA signals have no effect on the growth of the adenovirus.

MRK Ad5 HIV-1 gag exhibited the most desirable results. This construct contains the hCMV(no intron)-FLgag-bGHpA transgene inserted into the new E3+ adenovector backbone, MRKpAdHVE3, in the E1 parallel orientation. We have
10 designated this adenovector MRK Ad5 HIV-1 gag. This construct was prepared as outlined below:

The pre-plasmid MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA was digested with *PacI* to release the vector backbone and 3.3 µg was transfected by calcium phosphate method (Amersham Pharmacia Biotech.) in a 6 cm dish containing
15 PER.C6[®] cells at ~60% confluence. Once CPE was reached (7-10 days), the culture was freeze/thawed three times and the cell debris pelleted. 1 ml of this cell lysate was used to infect into a 6 cm dish containing PER.C6[®] cells at 80-90% confluence. Once CPE was reached, the culture was freeze/thawed three times and the cell debris pelleted. The cell lysate was then used to infect a 15 cm dish containing PER.C6[®]
20 cells at 80-90% confluence. This infection procedure was continued and expanded at passage 6. The virus was then extracted from the cell pellet by CsCl method. Two bandings were performed (3-gradient CsCl followed by a continuous CsCl gradient). Following the second banding, the virus was dialyzed in A105 buffer. Viral DNA was extracted using pronase treatment followed by phenol chloroform. The viral
25 DNA was then digested with *HindIII* and radioactively labeled with [³³P]dATP. Following gel electrophoresis to separate the digestion products the gel was dried down on Whatman paper and then subjected to autoradiography. The digestion products were compared with the digestion products from the pre-plasmid (that had been digested with *PacI/HindIII* prior to labeling). The expected sizes were
30 observed, indicating that the virus had been successfully rescued. This strategy was used to rescue virus from each of the various adenovector plasmid constructs prepared.

EXAMPLE 12

Stability Analyses

To determine whether the various adenovector constructs (e.g., MRK Ad5 HIV-1 gag) show genetic stability, the viruses were each passaged continually. The viral DNA was analyzed at passages 3, 6 and 10. Each virus maintained its correct genetic structure. In addition, the stability of the MRK Ad5 HIV-1 gag was analyzed under propagation conditions similar to that performed in large scale production. For this analysis, the transfections of MRK Ad5 HIV-1 gag as well as three other adenoviral vectors were repeated and the virus was purified at P3. The three other adenovectors were as follows: (1) that comprising hCMV(no intron)-Flgag with a bGHpA terminator in an E3- adenovector backbone; (2) that comprising hCMV(no intron)-Flgag with a SPA termination signal in an E3+ adenovector backbone, and that comprising a mCMV-Flgag with a bGHpA terminator in an E3+ adenovector backbone. All of the vectors have the transgene inserted in the E1 parallel orientation. Viral DNA was analyzed by radioactive restriction analysis to confirm that it was correct before being delivered to fermentation cell culture for continued passaging in serum-free media. At P5 each of the four viruses were purified and the viral DNA extracted for analysis by the restriction digestion and radiolabeling procedure. This virus has subsequently been used in a series of studies (*in vitro* gag expression in COS cells, rodent study and rhesus monkey study) as will be described below. The viruses from P5 are shown in Figure 9.

The passaging under serum-free conditions was continued for the MRKHVE3 (transgene-less, obtained from MRKpAdHVE3 pre-plasmid) and the MRKAd5HIV-1gag (obtained from MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA pre-plasmid) viruses. Figure 10 shows viral DNA analysis by radioactive restriction digestion at passage 11 for MRKHVE3, MRKAd5HIV-1gagE3-, and passage 11 and 12 for MRKAd5HIV-1gag. Aside from the first lane which is the DNA marker lane, the next three lanes are virus from the pre-plasmid controls (controls based on the original virus) - MRKpAdHVE3 (also referred to as "pMRKHVE3"), MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA, and pMRKAd5gag(E3-), respectively. As seen in Figure 10, each of the viral DNA samples show the expected bands with no extraneous bands showing. This signifies that there are no major variant adenovirus species present that can be detected by autoradiography.

Figure 11 shows the results of viral competition study between MRKHVE3 and MRKAd5HIV-1gag. These viruses were mixed together at equal MOI (140 viral

particles each; 280 vp total) at passage 6 and continued to be passaged until P11. Aside from the first lane which is the DNA marker lane, the next two lanes are the pre-plasmid controls obtained from MRKpAdHVE3 and MRKpAdHVE3+CMV(no intron)-FLgag-bGHPA. The next two lanes are the viral DNA from the starting viral material at passage six. The last two lanes are the competition studies performed in duplicate. The data in Figure 11 shows the effect the gag transgene in culture. Growth of a MRKAd5gag virus was compared with growth of a "transgene-less" MRKHVE3. These two viruses were infected at the same MOI (i.e. 140 vp each) at passage 6 and then passaged through to passage 11 and the viral pool was analyzed by radioactive restriction analysis. The data shows that one virus did not out compete the other. Therefore, the gag transgene did not show obvious signs of toxicity to the adenovirus.

Analysis by *HindIII* digestion shows that each virus specie is present in approximately equal amounts. As above, there does not appear to be signs of any extraneous bands. Figure 12 shows higher passage numbers for MRKAd5HIV-1gag grown under serum-containing conditions. The genome integrity again has been maintained and there is no evidence of rearrangements, even at the highest passage level (P21).

Each of the four vectors shown in Figure 9 were analyzed for amplification capacity. Table 4 below shows the QPA analysis used in the estimation of viral amplification ratios at P4. The determination of the amplification ratio for the original HIV-1 gag construct is based on the clinical lot at P12. It has been shown that amplification rates increases with higher passage number for the original virus. The reason for this observation is due to the emergence of variants which exhibit increased growth rates compared to the intact adenovector. With continued passaging of the original Ad gag vector, the level of variants increases and hence amplification rates increase also.

The MRK Ad5 HIV-1 gag virus has also been continually passaged under process conditions (i.e., serum-free media). Viral DNA extracted from passages 11 and 12 show no evidence of rearrangement.

Table 4:
Amplification Ratios Based on AEX and QPA Analysis of
Virus Amplification from Passage 3 to Passage 4.

Ad gag construct	Amplification Ratio
MRKAd5gag	470
HCMV-Flgag-bGHpA [E3-]	115
HCMV-Flgag-SPA [E3+]	320
mCMV-FLgag-bGHpA [E3+]	420
Original construct *	40 - 50

* This estimation is based on the clinical lot growth characteristics at Passage 12.

EXAMPLE 13

Analytical Evaluation of the enhanced Ad5 Constructs

To study the effects of the transgene and the E3 gene on virus amplification, the enhanced adenoviral vector, MRK Ad5 HIV-1 gag, along with its transgene-less version (MRKpAdHVE3) and its E3- version (MRK Ad5 HIV-1 gag E3-), was studied for several passages under serum-free conditions. Table 5A shows the amplification ratios determined for passages P3 to P8 for MRK Ad5 HIV-1 gag. Within a certain MOI range, it has been determined that the virus output is directly proportional to the virus input. Therefore, the greater the number of virus particles per cell at infection, the greater the virus amount produced. Viral amplification ratios, on the other hand, are inversely proportional to the virus input. The lower the virus input, the greater the amplification ratio.

Table 5B shows the amplification rates of the new E3+ vector backbone MRKpAdHVE3. It has a significantly lower rate of amplification compared with the gag transgene containing version. This may be contributed to the larger size MRK Ad5 HIV-1 gag since it contains the transgene. This inclusion of the transgene brings the size of the adenovirus closer to the size of a wild type Ad5 virus. It is well known that adenoviruses amplify best when they are at close to their wild type genomic size.

Wild type Ad5 is 35,935 bp. The MRKpAdHVE3 is 32,905 bp in length. The enhanced adenovector MRK Ad5 HIV-1 gag is 35,453bp (See Figure 14 for vector map; see also Figure 15A-X show the complete pre-adenoviral vector sequence, which includes an additional 2,021 bp of the vector backbone).

- 5 Table 5C shows the amplification rates of the new E3- gag containing virus MRK Ad5 HIV-1 gag E3-. Once again, this virus shows lower growth rate than the enhanced adenoviral vector. This may be attributed to the decreased sized of this virus (due to the E3 gene deletion) compared with wild type Ad5. The MRK Ad5 HIV-1 gag E3- virus is 32,810 bp in length. This can be compared with the wild type
- 10 Ad5 which is 35,935 bp and MRK Ad5 HIV-1 gag which is 35,453 bp in length.

Table 5A: Amplification ratios determined by AEX and QPA for MRKAd5gag over several continuous passaging in serum free media. Following P5, two replicate samples were taken (rep-1 and rep-2) and analyzed.

MRKAd5gag rep1

	Xv (10^6 cells/ml), Infection	Viability (%), Harvest	Harvest Time h.p.i.	Cell Passage Number	Titer 10^{10} vp/ml culture	Titer 10^6 vp/cell	QPA 10^6 TCID ₅₀ /ml	Ratio AEX:QPA	Amplification Ratio	AEX Internal Control
P4	1.48, 81%	0.58, 50%	44	45	8.7	5.9	1.72	50	470 (MOI = 125)	
P5	1.38, 93%	0.66, 47%	48	49	6.7	4.9	1.38	49	170	
P6	1.04, 94%	0.68, 77%	47	48	5.8	5.6	1.42	41	200	
P7	1.50, 84%	0.95, 61%	49.5	50	3.9	1.4	0.87	40	50	
P7	1.09, 97%	0.76, 59%	50	52	5.2	4.7	1.70	81	170	
P8	1.03, 94%	0.86, 64%	47.5	54	8.0	8.7	1.10	82	310	
P9	0.89, 95%	0.99, 73%	47.5	56	4.4	4.9	1.03	43	175	3.12 2.84
P10	1.09, 91%	1.06, 86%	47.5	58	8.0	2.8	1.16	28	100	2.70 2.60
P11	1.18, 88%	0.98, 65%	47	60	3.6	3.0	1.15	31	110	2.70 2.70
P12	0.98, 91%	0.85, 63%	47.5	47	5.4	5.5	1.20	45	200	2.86 2.60
P13	1.00, 88%	0.70, 67%	49	49	5.8	5.8	1.11	52	210	3.18 3.18
P14	1.94, 82%	0.88, 67%	46	53	8.6	4.4			160	3.28 3.27
P15	0.97, 96%	0.64, 66%	47	47	6.9	7.1			250	3.12 2.91

Table 5B: Amplification ratios determined by AEX and QPA for MRKHVE3 over several continuous passaging in serum free media. MRKHVE3 is the new vector backbone which does NOT carry a transgene.

MRKHVE3

	Xv (10^6 cells/ml), Infection	Viability (%), Harvest	Harvest Time h.p.i.	Cell Passage Number	Titer 10^{10} vp/ml culture	Titer 10^6 vp/cell	QPA 10^6 TCID ₅₀ /ml	Ratio AEX:QPA	Amplification Ratio	AEX Internal Control
P4	1.10, 97%	1.28, 78%	49	54	4.1	3.8	1.70	25	300 (MOI = 125)	
P5	0.82, 89%	1.18, 77%	47	48	4.3	4.7	1.24	35	170	
P6	1.55, 88%	1.26, 76%	49.5	50	1.2	0.8	0.58	21	30	
P6	1.09, 97%	1.11, 81%	49	52	4.0	3.6	1.16	34	130	
P7	1.17, 91%	1.22, 91%	47.5	54	3.7	3.2	0.50	74	110	
P8	0.98, 88%	1.41, 63%	48	56	2.1	2.1	0.47	45	75	3.12 2.84
P8	1.20, 89%	1.26, 81%	47.5	58	0.8	0.7	0.29	28	25	2.70 2.60
P10	0.89, 82%	1.55, 86%	47	60	2.3	2.3	0.43	53	80	2.70 2.70
P11	1.07, 86%	1.25, 83%	48	47	2.7	2.6	0.41	66	80	2.86 2.60
P12	0.80, 91%	1.14, 60%	49.5	48	5.9	7.4	0.48	123	280	3.18 3.18
P13	1.98, 85%	1.14, 65%	43.5	53	5.8	3.0			110	3.28 3.27
P14	0.97, 96%	1.03, 88%	48.5	47	9.4	8.7			350	3.12 2.91
P15	0.87, 89%	0.97, 69%	49.5	49	5.3	6.1			218	2.78 2.52

Table 5C. Amplification ratios determined by AEX and QPA for MRKAd5gag(E3-) over several continuous passaging in serum free media. This construct is identical to the MRKAd5gag construct except that this version is DELETED of the E3 gene.

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MRKAd5gag(E3-)

	Xv (10 ⁶ cells/ml), Infection	Viability (%), Harvest	Harvest Time h.p.i.	Cell Passage Number	Titer 10 ¹⁰ vp/ml culture	Titer 10 ⁴ vp/cell	QPA 10 ⁶ TCID ₅₀ /ml	Ratio AEX:QPA	Amplification Ratio	AEX Internal Control
P4	1.62, 77%	1.12, 62%	47.5	46	2.0	1.2	0.92	20	100 (MOI=125)	
P5	1.16, 82%	0.62, 43%	49	49	3.3	2.9	0.99	34	100	
P6	1.71, 86%	0.20, 10%	49	50	4.7	2.7	1.70	28	100	
P8	1.03, 97%	0.63, 64%	49.5	52	5.4	5.0	1.76	31	180	
P7	1.17, 91%	0.98, 72%	47.50	54	7.1	6.1	0.67	106	220	
P8	0.98, 88%	0.77, 48%	48	56	3.1	3.2	0.66	47	115	3.12
P9	1.20, 89%	1.03, 72%	48	58	1.8	1.5	0.57	32	55	2.84
P10	0.99, 82%	0.80, 62%	48.5	60	3.2	3.2	0.68	47	115	2.70
P11	1.07, 96%	0.88, 70%	48.5	47	5.9	5.5	0.68	87	200	2.60
P12	0.80, 81%	0.67, 59%	50	49	6.1	6.4	0.72	71	230	2.88
P13	1.96, 95%	0.91, 59%	45.5	53	7.4	3.8			135	2.60
P14	0.97, 96%	0.81, 74%	48	47	6.8	7.0			250	3.18
P15	0.87, 89%	0.84, 56%	49	49	4.8	5.5			196	3.18
										3.28
										3.27
										3.12
										2.91
										2.78
										2.52

EXAMPLE 14

Gag Expression Analysis of the Novel Constructs

In vitro gag analysis of the MRK Ad5 HIV-1 gag and the original HIV-gag vectors (research and clinical lot) show comparable gag expression. The clinical lot shows only a slightly reduced gag expression level. The most noticeable difference is with the mCMV vector. This vector shows roughly 3 fold lower expression levels compared with the other vectors tested (which all contain hCMV promoters). The mCMV-FLgag with bGHpA assay was performed three times using different propagation and purification lots and it consistently exhibited weaker gag expression.

EXAMPLE 15

Evaluation of MRK Ad5 HIV-1 gag and Other gag-Containing Adenovectors in Balb/c Mice

Cohorts of 10 balb/c mice were vaccinated intramuscularly with escalating doses of MRK Ad5 HIV-1 gag, and the research and clinical lots of original Ad5HIV-1gag. Serum samples were collected 3 weeks post dose 1 and analyzed by anti-p24 sandwich ELISA.

Anti-p24 titers in mice that received MRK Ad5 HIV-1 gag (10^7 and 10^9 vp(viral particle) doses) were comparable (Figure 13) to those of the research lot of Ad5HIV-1 gag, for which much of the early rhesus data were generated on. These titers were also comparable when E3 is deleted (MRKAd5hCMVgagbGHpA(E3-)) or SPA is substituted for bGHpA terminator (MRKAd5 hCMV-gag-SPA (E3+)) or murine CMV promoter is used in place of hCMV (MRKAd5 mCMV-gag-bGHpA (E3+)) in the MRKAd5 backbone.

The results shown in Table 7 indicate that the three other vectors (in addition to the preferred vector, MRK Ad5 HIV-1 gag, are also capable of inducing strong anti-gag antibody responses in mice. Interestingly enough, while the mCMV-FLgag construct containing bGHpA and E3+ in an E1 parallel orientation showed lowest gag expression in the COS cell *in vitro* infection (Table 6) in comparison with the other vectors tested, it generated the greatest anti-gag antibody response this *in vivo* Balb/c study. Table 7 also shows a dose response in anti-gag antibody production in both the research and the clinical lot. As expected, the clinical lot shows reduced anti-gag antibody induction at each dosage level compared to the same dosage used for the research lot.

Table 6: *In vitro* analysis for gag expression in COS cells by Elisa assay.

Viral Vectors ^a	$\mu\text{g gag}/4.8 \times 10^5 \text{ COS}/10^8 \text{ parts}/48\text{hr}$
MRKAd5gag ^b	1.40
Clinical lot Ad5gag ^c	1.28
Research lot Ad5gag ^d	1.32
MCMVFL-gagbGHpA ^e	0.42

^a $A_{260\text{nm}}$ absorbance readings taken for viral particle determinations.

^b MRKAd5gag was produced in serum free conditions and purified at P5.

^c Clinical lot# Ad5gagFN0001

^d Research Ad5FLgag lot# 6399

^e mCMVFL-gagbGHpA was produced in serum free conditions and purified at P5.

Table 7: mHIV020 Anti-p24 Ab Titers in Balb/c mice (n=10) vaccinated with various Adgag constructs and lots (3 week post dose1).

Group ID	Vaccine	Dose (vp)	GMT	SE upper	SE lower
1	^a MRKAd5gag	10 ⁷	25600	5877	4780
2	"	10 ⁹	409600	94028	76473
3	hCMV FL-gag bGHpA [E3-] →	10 ⁷	7352	2077	1620
4	"	10 ⁹	235253	59767	47659
5	hCMV FL-gag SPA [E3+] →	10 ⁷	12800	9905	236
6	"	10 ⁹	310419	99181	75165
7	^b mCMV FL-gag bGHpA [E3+] →	10 ⁷	44572	23504	15389
8	"	10 ⁹	941014	239068	190636
9	^c hCMV FL-gag bGHpA [E3-] ←	10 ⁷	3676	934	745
10	"	10 ⁹	117627	17491	15227
11	research lot hCMV intronA FL-gag bGHpA [E3-] <-	10 ⁶	528	262	175
12	"	10 ⁷	14703	5274	3882
13	"	10 ⁸	58813	14942	11915
14	"	10 ⁹	204800	53232	42250
15	clinical lot hCMVintronA FL-gag bGHpA [E3-] <-	10 ⁶	230	82	61
16	"	10 ⁷	4222	3405	1138
17	"	10 ⁸	19401	3939	3274
18	"	10 ⁹	89144	25187	19639
19	Naïve	none	93	7	6

*2x50 µL i.m. (quad) injections/animal

P.I.s: Youil, Chen, Casimiro

Vaccination: T. Toner, Q. Su

Assay: M. Chen

^aThe structure of MRKAd5gag is: hCMVFL-gagbGHpA [E3+] → The same lot of MRKAd5gag used in this rodent study was used in the Rhesus monkey study (Tables 7 and 8).

^bThe same lot of mCMVFL-gagbGHpA[E3+] used in the *in vitro* study (Table 6) was used here.

^cThis construct was designed by Volker Sandig. It contains a shorter version of the hCMV promoter than that used in the MRK constructs. The adenovector backbone is identical to the original backbone used in the original Adgag vector. Expression at 10e7 dose from this vector is 7 fold lower than the same dose of the MRKAd5gag and 4 fold lower than the research lot.

EXAMPLE 16

Comparison of Humoral and Cellular Responses Towards the Original Ad-gag Construct with the New MRK Ad5 HIV-1 gag in Rhesus Monkeys

- 5 Cohorts of 3 rhesus monkeys were vaccinated intramuscularly with MRK Ad5 HIV-1 gag or the clinical Ad5gag bulk at two doses, 10¹¹ vp and 10⁹ vp. Immunizations were conducted at week 0, 4, and 25. Serum and PBMC samples were collected at selected time points. The serum sample were assayed for anti-p24 Ab titers (using competitive based assay) and the PBMCs for antigen-specific IFN-
- 10 gamma secretion following overnight stimulation with gag 20-mer peptide pool (via ELISpot assay).

The results shown in Table 8 indicate comparable responses with respect to the generation of anti-gag antibodies. The frequencies of gag-specific T cells in

- peripheral blood assmumarized in Table 9 demonstrate a strong cellular immune response generated after a single dose with the new construct MRK Ad5 HIV-1 gag. The responses are also boostable with second dose of the same vector. The vector is also able to induce CD8+ T cell responses (as evident by remaining spot counts after
- 5 CD4+ depletion of PBMCs) which are responsible for cytotoxic activity.

Table 8 Anti-p24 antibody titers (in mMU/mL) in rhesus macaques immunized with gag-expressing adenovectors (Protocol HIV203).

Vaccine	Pre	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 25	Wk 28
MRKAd5gag ^a , 10 ¹¹ vp								
97N010	<10	118	5528	11523	7062	21997	ND	51593
97N116	<10	62	772	1447	1562	2174	ND	20029
98X007	<10	66	3353	6156	6845	3719	ND	24031
MRKAd5gag, 10 ⁹ vp								
97N120	<10	51	204	318	366	482	ND	6550
97N144	<10	18	118	274	706	888	ND	7136
98X008	<10	15	444	386	996	1072	ND	12851
Ad5gag ^b , Clinical Lot, 10 ¹¹ vp								
97X001	<10	87	2579	4718	7174	7250	ND	69226
97N146	<10	72	3604	7380	7526	18906	ND	60283
98X009	<10	78	4183	3946	3124	6956	ND	26226
Ad5gag, Clinical Lot, 10 ⁹ vp								
97N020	<10	<10	143	371	390	1821	ND	17177
97X003	<10	<10	39	93	156	596	ND	2053
98X012	<10	81	342	717	956	1558	ND	11861
^a MRKAd5gag (hCMV, bGHpA, E3+)								
^b original Ad5gag vector (hCMV/Intron A, bGHpA, E3-), lot#FN0001								
ND, not determined								

Table 9. Number of gag-specific T cells per million peripheral blood mononuclear cells (PBMCs) in rhesus monkeys immunized with gag-expressing adenovectors. Also included are those frequencies in PBMCs depleted of CD4⁺ T cells.

Grp #	Vaccination T=0,4,25 wks	Monkey ID	T=4 Wk		T=6 Wk		T=11 Wk		T=16 Wk		T=25 Wk		T=28 Wk	
			Media ^a	Gag H ^b	Media	Gag H	Media	Gag H	Media	Gag H	Media	Gag H	Media	Gag H
1	MRKAd5gag 10 ⁹ 11 vp	97ND10	6	89	0	395	0	1058	0	1174	3	775	4	1074
		97ND10(CD4-)	4	38			3	993			0	76	0	594
		97N116	1	398	1	609	0	534	4	395	1	261	0	408
		97N116(CD4-)	11	676			0	593			0	184	0	666
		98X007	10	579	0	1304	3	2193	1	2118	3	1588	0	2113
		98X007(CD4-)	20	965			0	2675			0	1656	0	1278
2	MRKAd5gag 10 ⁹ 9 vp	97N120	5	275	1	249	4	141	4	119	9	206	4	219
		97N120(CD4-)	11	170			0	85			0	75	1	219
		97N144	3	236	6	438	1	318	3	256	1	98	5	373
		97N144(CD4-)	6	148			0	285			ND	ND	0	625
		98X008	4	368	1	1090	3	891	4	673	3	473	5	735
		98X008(CD4-)	14	696			0	1175			0	391	4	848
3	Ad5gag clinical lot 10 ⁹ 11 vp	97X001	0	261	1	485	0	817	0	1220b	1	894	0	1858
		97X001(CD4-)	10	283			3	996			0	1010	0	1123
		97N146	3	150	1	465	0	339	1	1272	3	1238	3	1785
		97N146(CD4-)	6	133			0	370			0	654	0	971
		98X009	0	93	3	339	3	559	0	896	1	384	0	1748
		98X009(CD4-)	0	73			0	333			0	225	0	644
4	Ad5gag clinical lot 10 ⁹ 9 vp	97ND20	3	30	1	101	0	66	0	36	0	26	0	41
		97ND20(CD4-)	10	29			0	15			0	1	0	16
		97X003	4	68	5	134	0	18	1	38	4	38	6	81
		97X003(CD4-)	9	40			0	6			0	4	0	19
		98X012	5	95	3	54	1	34	0	18	0	20	1	121
		98X012(CD4-)	11	70			0	11			0	8	0	41
5	Naïve	96RD41	6	8	1	1	0	0	0	0	0	0	1	0
		053F	14	18	5	16	20	14	19	15	10	15	24	9

Based on either 4x10⁶ or 2x10⁶ cells per well (depending on spot density)

ND, not determined

^aMock or no peptide control

^bPool of 20-aa peptides overlapping by 10 aa and encompassing the gag sequence

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The adenovectors described herein and, particularly, MRK Ad5 HIV-1 gag, represent very promising HIV-gag adenovectors with respect to their enhanced growth characteristics in both serum and, more importantly, in serum-free media conditions. In comparison with the current HIV-1 gag adenovector construct, MRK Ad5 HIV-1 gag shows a 5-10 fold increased amplification rate. We have shown that it is genetically stable at passage 21. This construct is able to generate significant cellular immune responses *in vivo* even at a relatively low dose of 10⁹ vp. The potency of the MRKAd5gag construct is comparable to, if not better than the original HIV-1 gag vector as shown in this rhesus monkey study.

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EXAMPLE 17

CODON OPTIMIZED HIV-1 POL AND CODON OPTIMIZED HIV-1 POL MODIFICATIONS

The open reading frames for the various synthetic *pol* genes disclosed herein comprise coding sequences for the reverse transcriptase (or RT which consists of a polymerase and RNase H activity) and integrase (IN). The protein sequence is based

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on that of Hxb2r, a clonal isolate of IIB; this sequence has been shown to be closest to the consensus clade B sequence with only 16 nonidentical residues out of 848 (Korber, et al., 1998, Human retroviruses and AIDS, Los Alamos National Laboratory, Los Alamos, New Mexico). The skilled artisan will understand after review of this specification that any available HIV-1 or HIV-2 strain provides a potential template for the generation of HIV pol DNA vaccine constructs disclosed herein. It is further noted that the protease gene is excluded from the DNA vaccine constructs of the present invention to insure safety from any residual protease activity in spite of mutational inactivation. The design of the gene sequences for both wild-type (wt-pol) and inactivated pol (IA-pol) incorporates the use of human preferred ("humanized") codons for each amino acid residue in the sequence in order to maximize *in vivo* mammalian expression (Lathe, 1985, *J. Mol. Biol.* 183:1-12). As can be discerned by inspecting the codon usage in SEQ ID NOs: 1, 3, 5 and 7, the following codon usage for mammalian optimization is preferred: Met (ATG), Gly (GGC), Lys (AAG), Trp (TGG), Ser (TCC), Arg (AGG), Val (GTG), Pro (CCC), Thr (ACC), Glu (GAG); Leu (CTG), His (CAC), Ile (ATC), Asn (AAC), Cys (TGC), Ala (GCC), Gln (CAG), Phe (TTC) and Tyr (TAC). For an additional discussion relating to mammalian (human) codon optimization, see WO 97/31115 (PCT/US97/02294), which, as noted elsewhere in this specification, is hereby incorporated by reference. It is intended that the skilled artisan may use alternative versions of codon optimization or may omit this step when generating HIV pol vaccine constructs within the scope of the present invention. Therefore, the present invention also relates to non-codon optimized versions of DNA molecules and associated recombinant adenoviral HIV vaccines which encode the various wild type and modified forms of the HIV Pol protein disclosed herein. However, codon optimization of these constructs is a preferred embodiment of this invention.

A particular embodiment of this portion of the invention comprises codon optimized nucleotide sequences which encode wt-pol DNA constructs (herein, "wt-pol" or "wt-pol (codon optimized)") wherein DNA sequences encoding the protease (PR) activity are deleted, leaving codon optimized "wild type" sequences which encode RT (reverse transcriptase and RNase H activity) and IN integrase activity. A DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:1, the open reading frame being contained from an initiating Met residue at nucleotides 10-12 to a termination codon from nucleotides 2560-2562. SEQ ID NO:1 is as follows:

AGATCTACCA TGGCCCCCAT CTCCCCCATT GAGACTGTGC CTGTGAAGCT GAAGCCTGGC
ATGGATGGCC CCAAGGTGAA GCA GTGGCCC CTGACTGAGG AGAAGATCAA GGCCCTGGTG

GAAATCTGCA CTGAGATGGA GAAGGAGGGC AAAATCTCCA AGATTGGCCC CGAGAACCCC
TACAACACCC CTGTGTTTGC CATCAAGAAG AAGGACTCCA CCAAGTGGAG GAAGCTGGTG
GACTTCAGGG AGCTGAACAA GAGGACCCAG GACTTCTGGG AGGTGCAGCT GGGCATCCCC
CACCCCGCTG GCCTGAAGAA GAAGAAGTCT GTGACTGTGC TGGATGTGGG GGATGCCTAC
5 TTCTCTGTGC CCCTGGATGA GGACTTCAGG AAGTACACTG CCTTCACCAT CCCCTCCATC
AACAATGAGA CCCCTGGCAT CAGGTACCAG TACAATGTGC TGCCCCAGGG CTGGAAGGGC
TCCCCTGCCA TCTTCCAGTC CTCCATGACC AAGATCCTGG AGCCCTTCAG GAAGCAGAAC
CCTGACATTG TGATCTACCA GTACATGGAT GACCTGTATG TGGGCTCTGA CCTGGAGATT
GGGCAGCACA GGACCAAGAT TGAGGAGCTG AGGCAGCACC TGCTGAGGTG GGGCCTGACC
10 ACCCCTGACA AGAAGCACCA GAAGGAGCCC CCCTTCCTGT GGATGGGCTA TGAGCTGCAC
CCCGACAAGT GGACTGTGCA GCCCATTGTG CTGCCCTGAGA AGGACTCCTG GACTGTGAAT
GACATCCAGA AGCTGGTGGG CAAGCTGAAC TGGGCCTCCC AAATCTACCC TGGCATCAAG
GTGAGGCAGC TGTGCAAGCT GCTGAGGGGC ACCAAGGCCC TGACTGAGGT GATCCCCCTG
ACTGAGGAGG CTGAGCTGGA GCTGGCTGAG AACAGGGAGA TCCTGAAGGA GCCTGTGCAT
15 GGGGTGTACT ATGACCCCTC CAAGGACCTG ATTGCTGAGA TCCAGAAGCA GGGCCAGGGC
CAGTGGACCT ACCAAATCTA CCAGGAGCCC TTCAAGAACC TGAAGACTGG CAAGTATGCC
AGGATGAGGG GGGCCACAC CAATGATGTG AAGCAGCTGA CTGAGGCTGT GCAGAAGATC
ACCACTGAGT CCATTGTGAT CTGGGGCAAG ACCCCCAAGT TCAAGCTGCC CATCCAGAAG
GAGACCTGGG AGACCTGGTG GACTGAGTAC TGGCAGGCCA CCTGGATCCC TGAGTGGGAG
20 TTTGTGAACA CCCCCCCCCT GGTGAAGCTG TGGTACCAGC TGGAGAAGGA GCCCATTGTG
GGGGCTGAGA CCTTCTATGT GGATGGGGCT GCCAACAGGG AGACCAAGCT GGGCAAGGCT
GGCTATGTGA CCAACAGGGG CAGGCAGAAG GTGGTGACCC TGACTGACAC CACCAACCAG
AAGACTGAGC TCCAGGCCAT CTACCTGGCC CTCCAGGACT CTGGCCTGGA GGTGAACATT
GTGACTGACT CCCAGTATGC CCTGGGCATC ATCCAGGCCC AGCCTGATCA GTCTGAGTCT
25 GAGCTGGTGA ACCAGATCAT TGAGCAGCTG ATCAAGAAGG AGAAGGTGTA CCTGGCCTGG
GTGCCTGCCC ACAAGGGCAT TGGGGGCAAT GAGCAGGTGG ACAAGCTGGT GTCTGCTGGC
ATCAGGAAGG TGCTGTTCCCT GGATGGCATT GACAAGGCCC AGGATGAGCA TGAGAAGTAC
CACTCCAAC TGGAGGGCTAT GGCCTCTGAC TTCAACCTGC CCCCTGTGGT GGCTAAGGAG
ATTGTGGCCT CCTGTGACAA GTGCCAGCTG AAGGGGGAGG CCATGCATGG GCAGGTGGAC
30 TGCTCCCCCTG GCATCTGGCA GCTGGACTGC ACCCACCTGG AGGGCAAGGT GATCCTGGTG
GCTGTGCATG TGGCCTCCGG CTACATTGAG GCTGAGGTGA TCCCTGCTGA GACAGGCCAG
GAGACTGCCT ACTTCCTGCT GAAGCTGGCT GGCAGGTGGC CTGTGAAGAC CATCCACACT
GACAATGGCT CCAACTTCAC TGGGGCCACA GTGAGGGCTG CCTGCTGGTG GGCTGGCATC
AAGCAGGAGT TTGGCATCCC CTACAACCCC CAGTCCCAGG GGGTGGTGGA GTCCATGAAC
35 AAGGAGCTGA AGAAGATCAT TGGGCAGGTG AGGGACCAGG CTGAGCACCT GAAGACAGCT
GTGCAGATGG CTGTGTTTCAT CCACAACCTC AAGAGGAAGG GGGGCATCGG GGGCTACTCC

GCTGGGGAGA GGATTGTGGA CATCATTGCC ACAGACATCC AGACCAAGGA GCTCCAGAAG
 CAGATCACCA AGATCCAGAA CTCAGGGTG TACTACAGGG ACTCCAGGAA CCCCTGTGG
 AAGGGCCCTG CCAAGCTGCT GTGGAAGGGG GAGGGGGCTG TGGTGATCCA GGACAACTCT
 GACATCAAGG TGGTGCCCAG GAGGAAGGCC AAGATCATCA GGGACTATGG CAAGCAGATG
 5 GCTGGGGATG ACTGTGTGGC CTCCAGGCAG GATGAGGACT AAAGCCCGGG CAGATCT (SEQ
 ID NO:1).

The open reading frame of the wild type pol construct disclosed as SEQ ID
 NO:1 contains 850 amino acids, disclosed herein as SEQ ID NO:2, as follows:

Met Ala Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys Pro
 10 Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu Lys
 Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly Lys
 Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe Ala
 Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe Arg
 Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly Ile
 15 Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu Asp
 Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg Lys
 Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile
 Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala
 Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys Gln
 20 Asn Pro Asp Ile Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val Gly
 Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu Arg
 Gln His Leu Leu Arg Trp Gly Leu Thr Thr Pro Asp Lys Lys His Gln
 Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp Lys
 Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr Val
 25 Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln Ile
 Tyr Pro Gly Ile Lys Val Arg Gln Leu Cys Lys Leu Leu Arg Gly Thr
 Lys Ala Leu Thr Glu Val Ile Pro Leu Thr Glu Glu Ala Glu Leu Glu
 Leu Ala Glu Asn Arg Glu Ile Leu Lys Glu Pro Val His Gly Val Tyr
 Tyr Asp Pro Ser Lys Asp Leu Ile Ala Glu Ile Gln Lys Gln Gly Gln
 30 Gly Gln Trp Thr Tyr Gln Ile Tyr Gln Glu Pro Phe Lys Asn Leu Lys
 Thr Gly Lys Tyr Ala Arg Met Arg Gly Ala His Thr Asn Asp Val Lys
 Gln Leu Thr Glu Ala Val Gln Lys Ile Thr Thr Glu Ser Ile Val Ile
 Trp Gly Lys Thr Pro Lys Phe Lys Leu Pro Ile Gln Lys Glu Thr Trp
 Glu Thr Trp Trp Thr Glu Tyr Trp Gln Ala Thr Trp Ile Pro Glu Trp
 35 Glu Phe Val Asn Thr Pro Pro Leu Val Lys Leu Trp Tyr Gln Leu Glu
 Lys Glu Pro Ile Val Gly Ala Glu Thr Phe Tyr Val Asp Gly Ala Ala

Asn Arg Glu Thr Lys Leu Gly Lys Ala Gly Tyr Val Thr Asn Arg Gly
 Arg Gln Lys Val Val Thr Leu Thr Asp Thr Thr Asn Gln Lys Thr Glu
 Leu Gln Ala Ile Tyr Leu Ala Leu Gln Asp Ser Gly Leu Glu Val Asn
 Ile Val Thr Asp Ser Gln Tyr Ala Leu Gly Ile Ile Gln Ala Gln Pro
 5 Asp Gln Ser Glu Ser Glu Leu Val Asn Gln Ile Ile Glu Gln Leu Ile
 Lys Lys Glu Lys Val Tyr Leu Ala Trp Val Pro Ala His Lys Gly Ile
 Gly Gly Asn Glu Gln Val Asp Lys Leu Val Ser Ala Gly Ile Arg Lys
 Val Leu Phe Leu Asp Gly Ile Asp Lys Ala Gln Asp Glu His Glu Lys
 Tyr His Ser Asn Trp Arg Ala Met Ala Ser Asp Phe Asn Leu Pro Pro
 10 Val Val Ala Lys Glu Ile Val Ala Ser Cys Asp Lys Cys Gln Leu Lys
 Gly Glu Ala Met His Gly Gln Val Asp Cys Ser Pro Gly Ile Trp Gln
 Leu Asp Cys Thr His Leu Glu Gly Lys Val Ile Leu Val Ala Val His
 Val Ala Ser Gly Tyr Ile Glu Ala Glu Val Ile Pro Ala Glu Thr Gly
 Gln Glu Thr Ala Tyr Phe Leu Leu Lys Leu Ala Gly Arg Trp Pro Val
 15 Lys Thr Ile His Thr Asp Asn Gly Ser Asn Phe Thr Gly Ala Thr Val
 Arg Ala Ala Cys Trp Trp Ala Gly Ile Lys Gln Glu Phe Gly Ile Pro
 Tyr Asn Pro Gln Ser Gln Gly Val Val Glu Ser Met Asn Lys Glu Leu
 Lys Lys Ile Ile Gly Gln Val Arg Asp Gln Ala Glu His Leu Lys Thr
 Ala Val Gln Met Ala Val Phe Ile His Asn Phe Lys Arg Lys Gly Gly
 20 Ile Gly Gly Tyr Ser Ala Gly Glu Arg Ile Val Asp Ile Ile Ala Thr
 Asp Ile Gln Thr Lys Glu Leu Gln Lys Gln Ile Thr Lys Ile Gln Asn
 Phe Arg Val Tyr Tyr Arg Asp Ser Arg Asn Pro Leu Trp Lys Gly Pro
 Ala Lys Leu Leu Trp Lys Gly Glu Gly Ala Val Val Ile Gln Asp Asn
 Ser Asp Ile Lys Val Val Pro Arg Arg Lys Ala Lys Ile Ile Arg Asp
 25 Tyr Gly Lys Gln Met Ala Gly Asp Asp Cys Val Ala Ser Arg Gln Asp
 Glu Asp (SEQ ID NO:2).

The present invention especially relates to an adenoviral vector vaccine which
 comprises a codon optimized HIV-1 DNA pol construct wherein, in addition to
 deletion of the portion of the wild type sequence encoding the protease activity, a
 30 combination of active site residue mutations are introduced which are deleterious to
 HIV-1 pol (RT-RH-IN) activity of the expressed protein. Therefore, the present
 invention preferably relates to an adenoviral HIV-1 DNA pol-based vaccine wherein
 the construct is devoid of DNA sequences encoding any PR activity, as well as
 containing a mutation(s) which at least partially, and preferably substantially,
 35 abolishes RT, RNase and/or IN activity. One type of HIV-1 pol mutant which is part
 and parcel of an adenoviral vector vaccine may include but is not limited to a mutated

DNA molecule comprising at least one nucleotide substitution which results in a point mutation which effectively alters an active site within the RT, RNase and/or IN regions of the expressed protein, resulting in at least substantially decreased enzymatic activity for the RT, RNase H and/or IN functions of HIV-1 Pol. In a preferred embodiment of this portion of the invention, a HIV-1 DNA pol construct contains a mutation or mutations within the Pol coding region which effectively abolishes RT, RNase H and IN activity. An especially preferable HIV-1 DNA pol construct in a DNA molecule which contains at least one point mutation which alters the active site of the RT, RNase H and IN domains of Pol, such that each activity is at least substantially abolished. Such a HIV-1 Pol mutant will most likely comprise at least one point mutation in or around each catalytic domain responsible for RT, RNase H and IN activity, respectfully. To this end, an especially preferred HIV-1 DNA pol construct is exemplified herein and contains nine codon substitution mutations which results in an inactivated Pol protein (IA Pol: SEQ ID NO:4, Figure 17A-C) which has no PR, RT, RNase or IN activity, wherein three such point mutations reside within each of the RT, RNase and IN catalytic domains. Therefore, an especially preferred exemplification is an adenoviral vaccine which comprises, in an appropriate fashion, a DNA molecule which encodes IA-pol, which contains all nine mutations as shown below in Table 1. An additional preferred amino acid residue for substitution is Asp551, localized within the RNase domain of Pol. Any combination of the mutations disclosed herein may suitable and therefore may be utilized as an IA-Pol-based vaccine of the present invention. While addition and deletion mutations are contemplated and within the scope of the invention, the preferred mutation is a point mutation resulting in a substitution of the wild type amino acid with an alternative amino acid residue.

Table 1

	<u>wt aa</u>	<u>aa residue</u>	<u>mutant aa</u>	<u>enzyme function</u>
	Asp	112	Ala	RT
	Asp	187	Ala	RT
30	Asp	188	Ala	RT
	Asp	445	Ala	RNase H
	Glu	480	Ala	RNase H
	Asp	500	Ala	RNase H
	Asp	626	Ala	IN
35	Asp	678	Ala	IN
	Glu	714	Ala	IN

It is preferred that point mutations be incorporated into the IApol mutant adenoviral vaccines of the present invention so as to lessen the possibility of altering epitopes in and around the active site(s) of HIV-1 Pol.

5 To this end, SEQ ID NO:3 discloses the nucleotide sequence which codes for a codon optimized pol in addition to the nine mutations shown in Table 1, disclosed as follows, and referred to herein as "IApol":

```
AGATCTACCA TGGCCCCCAT CTCCCCCATT GAGACTGTGC CTGTGAAGCT GAAGCCTGGC
ATGGATGGCC CCAAGGTGAA GCAGTGGCCC CTGACTGAGG AGAAGATCAA GGCCCTGGTG
GAAATCTGCA CTGAGATGGA GAAGGAGGGC AAAATCTCCA AGATTGGCCC CGAGAACCCC
10 TACAACACCC CTGTGTTTGC CATCAAGAAG AAGGACTCCA CCAAGTGGAG GAAGCTGGTG
GACTTCAGGG AGCTGAACAA GAGGACCCAG GACTTCTGGG AGGTGCAGCT GGGCATCCCC
CACCCCGCTG GCCTGAAGAA GAAGAAGTCT GTGACTGTGC TGGCTGTGGG GGATGCCTAC
TTCTCTGTGC CCCTGGATGA GGACTTCAGG AAGTACACTG CCTTCACCAT CCCCTCCATC
AACAATGAGA CCCCTGGCAT CAGGTACCAG TACAATGTGC TGCCCCAGGG CTGGAAGGGC
15 TCCCCTGCCA TCTTCCAGTC CTCCATGACC AAGATCCTGG AGCCCTTCAG GAAGCAGAAC
CCTGACATTG TGATCTACCA GTACATGGCT GCCCTGTATG TGGGCTCTGA CCTGGAGATT
GGGCAGCACA GGACCAAGAT TGAGGAGCTG AGGCAGCACC TGCTGAGGTG GGGCCTGACC
ACCCCTGACA AGAAGCACCA GAAGGAGCCC CCCTTCTGTG GGATGGGCTA TGAGCTGCAC
CCCGACAAGT GGACTGTGCA GCCCATTGTG CTGCCTGAGA AGGACTCCTG GACTGTGAAT
20 GACATCCAGA AGCTGGTGGG CAAGCTGAAC TGGGCCTCCC AAATCTACCC TGGCATCAAG
GTGAGGCAGC TGTGCAAGCT GCTGAGGGGC ACCAAGGCCC TGACTGAGGT GATCCCCCTG
ACTGAGGAGG CTGAGCTGGA GCTGGCTGAG AACAGGGAGA TCCTGAAGGA GCCTGTGCAT
GGGGTGTACT ATGACCCCTC CAAGGACCTG ATTGCTGAGA TCCAGAAGCA GGGCCAGGGC
CAGTGGACCT ACCAAATCTA CCAGGAGCCC TTCAAGAACC TGAAGACTGG CAAGTATGCC
25 AGGATGAGGG GGGCCACAC CAATGATGTG AAGCAGCTGA CTGAGGCTGT GCAGAAGATC
ACCACTGAGT CCATTGTGAT CTGGGGCAAG ACCCCCAAGT TCAAGCTGCC CATCCAGAAG
GAGACCTGGG AGACCTGGTG GACTGAGTAC TGGCAGGCCA CCTGGATCCC TGAGTGGGAG
TTTGTGAACA CCCCCCCCCT GGTGAAGCTG TGGTACCAGC TGGAGAAGGA GCCCATTGTG
GGGGCTGAGA CTTTCTATGT GGCTGGGGCT GCCAACAGGG AGACCAAGCT GGGCAAGGCT
30 GGCTATGTGA CCAACAGGGG CAGGCAGAAG GTGGTGACCC TGACTGACAC CACCAACCAG
AAGACTGCCC TCCAGGCCAT CTACCTGGCC CTCCAGGACT CTGGCCTGGA GGTGAACATT
GTGACTGCCT CCCAGTATGC CCTGGGCATC ATCCAGGCCC AGCCTGATCA GTCTGAGTCT
GAGCTGGTGA ACCAGATCAT TGAGCAGCTG ATCAAGAAGG AGAAGGTGTA CCTGGCCTGG
GTGCCTGCCC ACAAGGGCAT TGGGGGCAAT GAGCAGGTGG ACAAGCTGGT GTCTGTCTGGC
35 ATCAGGAAGG TGCTGTTCCCT GGATGGCATT GACAAGGCCC AGGATGAGCA TGAGAAGTAC
CACTCCAACT GGAGGGCTAT GGCTCTGAC TTCAACCTGC CCCCTGTGGT GGCTAAGGAG
```

ATTGTGGCCT CCTGTGACAA GTGCCAGCTG AAGGGGGAGG CCATGCATGG GCAGGTGGAC
 TGCTCCCCTG GCATCTGGCA GCTGGCCTGC ACCCACCTGG AGGGCAAGGT GATCCTGGTG
 GCTGTGCATG TGGCCTCCGG CTACATTGAG GCTGAGGTGA TCCCTGCTGA GACAGGCCAG
 GAGACTGCCT ACTTCCTGCT GAAGCTGGCT GGCAGGTGGC CTGTGAAGAC CATCCACACT
 5 GCCAATGGCT CCAACTTCAC TGGGGCCACA GTGAGGGCTG CCTGCTGGTG GGCTGGCATC
 AAGCAGGAGT TTGGCATCCC CTACAACCCC CAGTCCCAGG GGGTGGTGGC CTCCATGAAC
 AAGGAGCTGA AGAAGATCAT TGGGCAGGTG AGGGACCAGG CTGAGCACCT GAAGACAGCT
 GTGCAGATGG CTGTGTTTCAT CCACAACCTC AAGAGGAAGG GGGGCATCGG GGGCTACTCC
 GCTGGGGAGA GGATTGTGGA CATCATTGCC ACAGACATCC AGACCAAGGA GCTCCAGAAG
 10 CAGATCACCA AGATCCAGAA CTTCAGGGTG TACTACAGGG ACTCCAGGAA CCCCCTGTGG
 AAGGGCCCTG CCAAGCTGCT GTGGAAGGGG GAGGGGGCTG TGGTGATCCA GGACAACTCT
 GACATCAAGG TGGTGCCCAG GAGGAAGGCC AAGATCATCA GGGACTATGG CAAGCAGATG
 GCTGGGGATG ACTGTGTGGC CTCCAGGCAG GATGAGGACT AAAGCCCGGG CAGATCT (SEQ ID
 NO:3) .

15 In order to produce the IA-pol-based adenoviral vaccines of the present
 invention, inactivation of the enzymatic functions was achieved by replacing a total of
 nine active site residues from the enzyme subunits with alanine side-chains. As
 shown in Table 1, all residues that comprise the catalytic triad of the polymerase,
 namely Asp112, Asp187, and Asp188, were substituted with alanine (Ala) residues
 20 (Larder, et al., *Nature* 1987, 327: 716-717; Larder, et al., 1989, *Proc. Natl. Acad. Sci.*
 1989, 86: 4803-4807). Three additional mutations were introduced at Asp445,
 Glu480 and Asp500 to abolish RNase H activity (Asp551 was left unchanged in this
 IA Pol construct), with each residue being substituted for an Ala residue, respectively
 (Davies, et al., 1991, *Science* 252:, 88-95; Schatz, et al., 1989, *FEBS Lett.* 257: 311-
 25 314; Mizrahi, et al., 1990, *Nucl. Acids. Res.* 18: pp. 5359-5353). HIV pol integrase
 function was abolished through three mutations at Asp626, Asp678 and Glu714.
 Again, each of these residues has been substituted with an Ala residue (Wiskerchen,
 et al., 1995, *J. Virol.* 69: 376-386; Leavitt, et al., 1993, *J. Biol. Chem.* 268: 2113-
 2119). Amino acid residue Pro3 of SEQ ID NO:4 marks the start of the RT gene.
 30 The complete amino acid sequence of IA-Pol is disclosed herein as SEQ ID NO:4 and
 Figure 17A-C, as follows:

35 Met Ala Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys Pro
 Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu Lys
 Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly Lys
 Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe Ala
 Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe Arg

Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly Ile
Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu Ala
Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg Lys
Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile
5 Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala
Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys Gln
Asn Pro Asp Ile Val Ile Tyr Gln Tyr Met Ala Ala Leu Tyr Val Gly
Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu Arg
Gln His Leu Leu Arg Trp Gly Leu Thr Thr Pro Asp Lys Lys His Gln
10 Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp Lys
Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr Val
Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln Ile
Tyr Pro Gly Ile Lys Val Arg Gln Leu Cys Lys Leu Leu Arg Gly Thr
Lys Ala Leu Thr Glu Val Ile Pro Leu Thr Glu Glu Ala Glu Leu Glu
15 Leu Ala Glu Asn Arg Glu Ile Leu Lys Glu Pro Val His Gly Val Tyr
Tyr Asp Pro Ser Lys Asp Leu Ile Ala Glu Ile Gln Lys Gln Gly Gln
Gly Gln Trp Thr Tyr Gln Ile Tyr Gln Glu Pro Phe Lys Asn Leu Lys
Thr Gly Lys Tyr Ala Arg Met Arg Gly Ala His Thr Asn Asp Val Lys
Gln Leu Thr Glu Ala Val Gln Lys Ile Thr Thr Glu Ser Ile Val Ile
20 Trp Gly Lys Thr Pro Lys Phe Lys Leu Pro Ile Gln Lys Glu Thr Trp
Glu Thr Trp Trp Thr Glu Tyr Trp Gln Ala Thr Trp Ile Pro Glu Trp
Glu Phe Val Asn Thr Pro Pro Leu Val Lys Leu Trp Tyr Gln Leu Glu
Lys Glu Pro Ile Val Gly Ala Glu Thr Phe Tyr Val Ala Gly Ala Ala
Asn Arg Glu Thr Lys Leu Gly Lys Ala Gly Tyr Val Thr Asn Arg Gly
25 Arg Gln Lys Val Val Thr Leu Thr Asp Thr Thr Asn Gln Lys Thr Ala
Leu Gln Ala Ile Tyr Leu Ala Leu Gln Asp Ser Gly Leu Glu Val Asn
Ile Val Thr Ala Ser Gln Tyr Ala Leu Gly Ile Ile Gln Ala Gln Pro
Asp Gln Ser Glu Ser Glu Leu Val Asn Gln Ile Ile Glu Gln Leu Ile
Lys Lys Glu Lys Val Tyr Leu Ala Trp Val Pro Ala His Lys Gly Ile
30 Gly Gly Asn Glu Gln Val Asp Lys Leu Val Ser Ala Gly Ile Arg Lys
Val Leu Phe Leu Asp Gly Ile Asp Lys Ala Gln Asp Glu His Glu Lys
Tyr His Ser Asn Trp Arg Ala Met Ala Ser Asp Phe Asn Leu Pro Pro
Val Val Ala Lys Glu Ile Val Ala Ser Cys Asp Lys Cys Gln Leu Lys
Gly Glu Ala Met His Gly Gln Val Asp Cys Ser Pro Gly Ile Trp Gln
35 Leu Ala Cys Thr His Leu Glu Gly Lys Val Ile Leu Val Ala Val His
Val Ala Ser Gly Tyr Ile Glu Ala Glu Val Ile Pro Ala Glu Thr Gly

Gln Glu Thr Ala Tyr Phe Leu Leu Lys Leu Ala Gly Arg Trp Pro Val
 Lys Thr Ile His Thr Ala Asn Gly Ser Asn Phe Thr Gly Ala Thr Val
 Arg Ala Ala Cys Trp Trp Ala Gly Ile Lys Gln Glu Phe Gly Ile Pro
 Tyr Asn Pro Gln Ser Gln Gly Val Val Ala Ser Met Asn Lys Glu Leu
 5 Lys Lys Ile Ile Gly Gln Val Arg Asp Gln Ala Glu His Leu Lys Thr
 Ala Val Gln Met Ala Val Phe Ile His Asn Phe Lys Arg Lys Gly Gly
 Ile Gly Gly Tyr Ser Ala Gly Glu Arg Ile Val Asp Ile Ile Ala Thr
 Asp Ile Gln Thr Lys Glu Leu Gln Lys Gln Ile Thr Lys Ile Gln Asn
 Phe Arg Val Tyr Tyr Arg Asp Ser Arg Asn Pro Leu Trp Lys Gly Pro
 10 Ala Lys Leu Leu Trp Lys Gly Glu Gly Ala Val Val Ile Gln Asp Asn
 Ser Asp Ile Lys Val Val Pro Arg Arg Lys Ala Lys Ile Ile Arg Asp
 Tyr Gly Lys Gln Met Ala Gly Asp Asp Cys Val Ala Ser Arg Gln Asp
 Glu Asp (SEQ ID NO:4).

As noted above, it will be understood that any combination of the mutations
 15 disclosed above may be suitable and therefore be utilized as an IA-pol-based
 adenoviral HIV vaccine of the present invention, either when administered alone or in
 a combined modality regime and/or a prime-boost regimen. For example, it may be
 possible to mutate only 2 of the 3 residues within the respective reverse transcriptase,
 RNase-H, and integrase coding regions while still abolishing these enzymatic
 20 activities. However, the IA-pol construct described above and disclosed as SEQ ID
 NO:3, as well as the expressed protein (SEQ ID NO:4;) is preferred. It is also
 preferred that at least one mutation be present in each of the three catalytic domains.

Another aspect of this portion of the invention are codon optimized HIV-1
 Pol-based vaccine constructions which comprise a eukaryotic trafficking signal
 25 peptide such as from tPA (tissue-type plasminogen activator) or by a leader peptide
 such as is found in highly expressed mammalian proteins such as immunoglobulin
 leader peptides. Any functional leader peptide may be tested for efficacy. However,
 a preferred embodiment of the present invention, as with HIV-1 Nef constructs shown
 herein, is to provide for a HIV-1 Pol mutant adenoviral vaccine construction wherein
 30 the pol coding region or a portion thereof is operatively linked to a leader peptide,
 preferably a leader peptide from human tPA. In other words, a codon optimized
 HIV-1 Pol mutant such as IA-Pol (SEQ ID NO:4) may also comprise a leader peptide
 at the amino terminal portion of the protein, which may effect cellular trafficking and
 hence, immunogenicity of the expressed protein within the host cell. As noted in
 35 Figure 16A-B, a DNA vector which may be utilized to practice the present invention
 may be modified by known recombinant DNA methodology to contain a leader signal

peptide of interest, such that downstream cloning of the modified HIV-1 protein of interest results in a nucleotide sequence which encodes a modified HIV-1 tPA/Pol protein. In the alternative, as noted above, insertion of a nucleotide sequence which encodes a leader peptide may be inserted into a DNA vector housing the open reading frame for the Pol protein of interest. Regardless of the cloning strategy, the end result is a polynucleotide vaccine which comprises vector components for effective gene expression in conjunction with nucleotide sequences which encode a modified HIV-1 Pol protein of interest, including but not limited to a HIV-1 Pol protein which contains a leader peptide. The amino acid sequence of the human tPA leader utilized herein is as follows: MDAMKRGLCCVLLLCGAVFVSPSEISS (SEQ ID NO:17). Therefore, another aspect of the present invention is to generate HIV-1 Pol-based vaccine constructions which comprise a eukaryotic trafficking signal peptide such as from tPA. To this end, the present invention relates to a DNA molecule which encodes a codon optimized wt-pol DNA construct wherein the protease (PR) activity is deleted and a human tPA leader sequence is fused to the 5' end of the coding region. A DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:5, the open reading frame disclosed herein as SEQ ID NO:6.

To this end, the present invention relates to a DNA molecule which encodes a codon optimized wt-pol DNA construct wherein the protease (PR) activity is deleted and a human tPA leader sequence is fused to the 5' end of the coding region (herein, "tPA-wt-pol"). A DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:5, the open reading frame being contained from an initiating Met residue at nucleotides 8-10 to a termination codon from nucleotides 2633-2635. SEQ ID NO:5 is as follows:

25 GATCACCATG GATGCAATGA AGAGAGGGCT CTGCTGTGTG CTGCTGCTGT GTGGAGCAGT
CTTCGTTTCG CCCAGCGAGA TCTCCGCCCC CATCTCCCCC ATTGAGACTG TGCCTGTGAA
GCTGAAGCCT GGCATGGATG GCCCCAAGGT GAAGCAGTGG CCCCTGACTG AGGAGAAGAT
CAAGGCCCTG GTGGAAATCT GCACTGAGAT GGAGAAGGAG GGCAAAATCT CCAAGATTGG
CCCCGAGAAC CCCTACAACA CCCCTGTGTT TGCCATCAAG AAGAAGGACT CCACCAAGTG
30 GAGGAAGCTG GTGGACTTCA GGGAGCTGAA CAAGAGGACC CAGGACTTCT GGGAGGTGCA
GCTGGGCATC CCCCACCCCG CTGGCCTGAA GAAGAAGAAG TCTGTGACTG TGCTGGATGT
GGGGGATGCC TACTTCTCTG TGCCCCCTGGA TGAGGACTTC AGGAAGTACA CTGCCTTCAC
CATCCCCCTCC ATCAACAATG AGACCCCTGG CATCAGGTAC CAGTACAATG TGCTGCCCCA
GGGCTGGAAG GGCTCCCCCTG CCATCTTCCA GTCTCCATG ACCAAGATCC TGGAGCCCTT
35 CAGGAAGCAG AACCTTGACA TTGTGATCTA CCAGTACATG GATGACCTGT ATGTGGGCTC
TGACCTGGAG ATTGGGCAGC ACAGGACCAA GATTGAGGAG CTGAGGCAGC ACCTGCTGAG

GTGGGGCCTG ACCACCCCTG ACAAGAAGCA CCAGAAGGAG CCCCCCTTCC TGTGGATGGG
 CTATGAGCTG CACCCCGACA AGTGGACTGT GCAGCCCATT GTGCTGCCTG AGAAGGACTC
 CTGGACTGTG AATGACATCC AGAAGCTGGT GGGCAAGCTG AACTGGGCCT CCCAAATCTA
 CCCTGGCATC AAGGTGAGGC AGCTGTGCAA GCTGCTGAGG GGCACCAAGG CCCTGACTGA
 5 GGTGATCCCC CTGACTGAGG AGGCTGAGCT GGAGCTGGCT GAGAACAGGG AGATCCTGAA
 GGAGCCTGTG CATGGGGTGT ACTATGACCC CTCCAAGGAC CTGATTGCTG AGATCCAGAA
 GCAGGGCCAG GGCCAGTGGA CCTACCAAAT CTACCAGGAG CCCTTCAAGA ACCTGAAGAC
 TGGCAAGTAT GCCAGGATGA GGGGGGCCCA CACCAATGAT GTGAAGCAGC TGACTGAGGC
 TGTGCAGAAG ATCACCCTG AGTCCATTGT GATCTGGGGC AAGACCCCCA AGTTCAAGCT
 10 GCCCATCCAG AAGGAGACCT GGGAGACCTG GTGGACTGAG TACTGGCAGG CCACCTGGAT
 CCCTGAGTGG GAGTTTGTGA ACACCCCCC CCTGGTGAAG CTGTGGTACC AGCTGGAGAA
 GGAGCCCATT GTGGGGGCTG AGACCTTCTA TGTGGATGGG GCTGCCAACA GGGAGACCAA
 GCTGGGCAAG GCTGGCTATG TGACCAACAG GGCAGGCAG AAGGTGGTGA CCCTGACTGA
 CACCACCAAC CAGAAGACTG AGCTCCAGGC CATCTACCTG GCCCTCCAGG ACTCTGGCCT
 15 GGAGGTGAAC ATTGTGACTG ACTCCCAGTA TGCCCTGGGC ATCATCCAGG CCCAGCCTGA
 TCAGTCTGAG TCTGAGCTGG TGAACCAGAT CATTGAGCAG CTGATCAAGA AGGAGAAGGT
 GTACCTGGCC TGGGTGCCTG CCCACAAGGG CATTGGGGGC AATGAGCAGG TGGACAAGCT
 GGTGTCTGCT GGCATCAGGA AGGTGCTGTT CCTGGATGGC ATTGACAAGG CCCAGGATGA
 GCATGAGAAG TACCACTCCA ACTGGAGGGC TATGGCCTCT GACTTCAACC TGCCCCCTGT
 20 GGTGGCTAAG GAGATTGTGG CCTCCTGTGA CAAGTGCCAG CTGAAGGGGG AGGCCATGCA
 TGGGCAGGTG GACTGCTCCC CTGGCATCTG GCAGCTGGAC TGCACCCACC TGGAGGGCAA
 GGTGATCCTG GTGGCTGTGC ATGTGGCCTC CGGCTACATT GAGGCTGAGG TGATCCCTGC
 TGAGACAGGC CAGGAGACTG CCTACTTCCT GCTGAAGCTG GCTGGCAGGT GGCCTGTGAA
 GACCATCCAC ACTGACAATG GCTCCAACCT CACTGGGGCC ACAGTGAGGG CTGCCTGCTG
 25 GTGGGCTGGC ATCAAGCAGG AGTTTGGCAT CCCCTACAAC CCCCAGTCCC AGGGGGTGGT
 GGAGTCCATG AACAAGGAGC TGAAGAAGAT CATTGGGCAG GTGAGGGACC AGGCTGAGCA
 CCTGAAGACA GCTGTGCAGA TGGCTGTGTT CATCCACAAC TTCAAGAGGA AGGGGGGCAT
 CGGGGGCTAC TCCGCTGGGG AGAGGATTGT GGACATCATT GCCACAGACA TCCAGACCAA
 GGAGCTCCAG AAGCAGATCA CCAAGATCCA GAACTTCAGG GTGTACTACA GGGACTCCAG
 30 GAACCCCTG TGGAAGGGCC CTGCCAAGCT GCTGTGGAAG GGGGAGGGGG CTGTGGTGAT
 CCAGGACAAC TCTGACATCA AGGTGGTGCC CAGGAGGAAG GCCAAGATCA TCAGGGACTA
 TGGCAAGCAG ATGGCTGGGG ATGACTGTGT GGCCTCCAGG CAGGATGAGG ACTAAAGCCC
 GGGCAGATCT (SEQ ID NO:5).

The open reading frame of the wild type tPA-pol construct disclosed as SEQ
 35 ID NO:5 contains 875 amino acids, disclosed herein as SEQ ID NO:6, as follows:
 Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly

Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ala Pro Ile Ser Pro Ile
Glu Thr Val Pro Val Lys Leu Lys Pro Gly Met Asp Gly Pro Lys Val
Lys Gln Trp Pro Leu Thr Glu Glu Lys Ile Lys Ala Leu Val Glu Ile
Cys Thr Glu Met Glu Lys Glu Gly Lys Ile Ser Lys Ile Gly Pro Glu
5 Asn Pro Tyr Asn Thr Pro Val Phe Ala Ile Lys Lys Lys Asp Ser Thr
Lys Trp Arg Lys Leu Val Asp Phe Arg Glu Leu Asn Lys Arg Thr Gln
Asp Phe Trp Glu Val Gln Leu Gly Ile Pro His Pro Ala Gly Leu Lys
Lys Lys Lys Ser Val Thr Val Leu Asp Val Gly Asp Ala Tyr Phe Ser
Val Pro Leu Asp Glu Asp Phe Arg Lys Tyr Thr Ala Phe Thr Ile Pro
10 Ser Ile Asn Asn Glu Thr Pro Gly Ile Arg Tyr Gln Tyr Asn Val Leu
Pro Gln Gly Trp Lys Gly Ser Pro Ala Ile Phe Gln Ser Ser Met Thr
Lys Ile Leu Glu Pro Phe Arg Lys Gln Asn Pro Asp Ile Val Ile Tyr
Gln Tyr Met Asp Asp Leu Tyr Val Gly Ser Asp Leu Glu Ile Gly Gln
His Arg Thr Lys Ile Glu Glu Leu Arg Gln His Leu Leu Arg Trp Gly
15 Leu Thr Thr Pro Asp Lys Lys His Gln Lys Glu Pro Pro Phe Leu Trp
Met Gly Tyr Glu Leu His Pro Asp Lys Trp Thr Val Gln Pro Ile Val
Leu Pro Glu Lys Asp Ser Trp Thr Val Asn Asp Ile Gln Lys Leu Val
Gly Lys Leu Asn Trp Ala Ser Gln Ile Tyr Pro Gly Ile Lys Val Arg
Gln Leu Cys Lys Leu Leu Arg Gly Thr Lys Ala Leu Thr Glu Val Ile
20 Pro Leu Thr Glu Glu Ala Glu Leu Glu Leu Ala Glu Asn Arg Glu Ile
Leu Lys Glu Pro Val His Gly Val Tyr Tyr Asp Pro Ser Lys Asp Leu
Ile Ala Glu Ile Gln Lys Gln Gly Gln Gly Gln Trp Thr Tyr Gln Ile
Tyr Gln Glu Pro Phe Lys Asn Leu Lys Thr Gly Lys Tyr Ala Arg Met
Arg Gly Ala His Thr Asn Asp Val Lys Gln Leu Thr Glu Ala Val Gln
25 Lys Ile Thr Thr Glu Ser Ile Val Ile Trp Gly Lys Thr Pro Lys Phe
Lys Leu Pro Ile Gln Lys Glu Thr Trp Glu Thr Trp Trp Thr Glu Tyr
Trp Gln Ala Thr Trp Ile Pro Glu Trp Glu Phe Val Asn Thr Pro Pro
Leu Val Lys Leu Trp Tyr Gln Leu Glu Lys Glu Pro Ile Val Gly Ala
Glu Thr Phe Tyr Val Asp Gly Ala Ala Asn Arg Glu Thr Lys Leu Gly
30 Lys Ala Gly Tyr Val Thr Asn Arg Gly Arg Gln Lys Val Val Thr Leu
Thr Asp Thr Thr Asn Gln Lys Thr Glu Leu Gln Ala Ile Tyr Leu Ala
Leu Gln Asp Ser Gly Leu Glu Val Asn Ile Val Thr Asp Ser Gln Tyr
Ala Leu Gly Ile Ile Gln Ala Gln Pro Asp Gln Ser Glu Ser Glu Leu
Val Asn Gln Ile Ile Glu Gln Leu Ile Lys Lys Glu Lys Val Tyr Leu
35 Ala Trp Val Pro Ala His Lys Gly Ile Gly Gly Asn Glu Gln Val Asp
Lys Leu Val Ser Ala Gly Ile Arg Lys Val Leu Phe Leu Asp Gly Ile

Asp Lys Ala Gln Asp Glu His Glu Lys Tyr His Ser Asn Trp Arg Ala
 Met Ala Ser Asp Phe Asn Leu Pro Pro Val Val Ala Lys Glu Ile Val
 Ala Ser Cys Asp Lys Cys Gln Leu Lys Gly Glu Ala Met His Gly Gln
 Val Asp Cys Ser Pro Gly Ile Trp Gln Leu Asp Cys Thr His Leu Glu
 5 Gly Lys Val Ile Leu Val Ala Val His Val Ala Ser Gly Tyr Ile Glu
 Ala Glu Val Ile Pro Ala Glu Thr Gly Gln Glu Thr Ala Tyr Phe Leu
 Leu Lys Leu Ala Gly Arg Trp Pro Val Lys Thr Ile His Thr Asp Asn
 Gly Ser Asn Phe Thr Gly Ala Thr Val Arg Ala Ala Cys Trp Trp Ala
 Gly Ile Lys Gln Glu Phe Gly Ile Pro Tyr Asn Pro Gln Ser Gln Gly
 10 Val Val Glu Ser Met Asn Lys Glu Leu Lys Lys Ile Ile Gly Gln Val
 Arg Asp Gln Ala Glu His Leu Lys Thr Ala Val Gln Met Ala Val Phe
 Ile His Asn Phe Lys Arg Lys Gly Gly Ile Gly Gly Tyr Ser Ala Gly
 Glu Arg Ile Val Asp Ile Ile Ala Thr Asp Ile Gln Thr Lys Glu Leu
 Gln Lys Gln Ile Thr Lys Ile Gln Asn Phe Arg Val Tyr Tyr Arg Asp
 15 Ser Arg Asn Pro Leu Trp Lys Gly Pro Ala Lys Leu Leu Trp Lys Gly
 Glu Gly Ala Val Val Ile Gln Asp Asn Ser Asp Ile Lys Val Val Pro
 Arg Arg Lys Ala Lys Ile Ile Arg Asp Tyr Gly Lys Gln Met Ala Gly
 Asp Asp Cys Val Ala Ser Arg Gln Asp Glu Asp (SEQ ID NO:6) .

The present invention also relates to a codon optimized HIV-1 Pol mutant
 20 contained within a recombinant adenoviral vector such as IA-Pol (SEQ ID NO:4)
 which comprises a leader peptide at the amino terminal portion of the protein, which
 may effect cellular trafficking and hence, immunogenicity of the expressed protein
 within the host cell. Any such adenoviral-based HIV-1 DNA pol mutant disclosed in
 the above paragraphs is suitable for fusion downstream of a leader peptide, such as a
 25 leader peptide including but not limited to the human tPA leader sequence. Therefore,
 any such leader peptide-based HIV-1 pol mutant construct may include but is not
 limited to a mutated DNA molecule which effectively alters the catalytic activity of
 the RT, RNase and/or IN region of the expressed protein, resulting in at least
 substantially decreased enzymatic activity one or more of the RT, RNase H and/or IN
 30 functions of HIV-1 Pol. In a preferred embodiment of this portion of the invention, a
 leader peptide/HIV-1 DNA pol construct contains a mutation or mutations within the
 Pol coding region which effectively abolishes RT, RNase H and IN activity. An
 especially preferable HIV-1 DNA pol construct is a DNA molecule which contains at
 least one point mutation which alters the active site and catalytic activity within the
 35 RT, RNase H and IN domains of Pol, such that each activity is at least substantially
 abolished, and preferably totally abolished. Such a HIV-1 Pol mutant will most likely

comprise at least one point mutation in or around each catalytic domain responsible for RT, RNase H and IN activity, respectfully. An especially preferred embodiment of this portion of the invention relates to a human tPA leader fused to the IA-Pol protein comprising the nine mutations shown in Table 1. The DNA molecule is disclosed
 5 herein as SEQ ID NO:7 and the expressed tPA-IA Pol protein comprises a fusion junction as shown in Figure 18. The complete amino acid sequence of the expressed protein is set forth in SEQ ID NO:8. To this end, SEQ ID NO:7 discloses the nucleotide sequence which codes for a human tPA leader fused to the IA Pol protein comprising the nine mutations shown in Table 1 (herein, "tPA-opt-IApol"). The open
 10 reading frame begins with the initiating Met (nucleotides 8-10) and terminates with a "TAA" codon at nucleotides 2633-2635. The nucleotide sequence encoding tPA-IAPol is also disclosed as follows:

GATCACCATG GATGCAATGA AGAGAGGGCT CTGCTGTGTG CTGCTGCTGT GTGGAGCAGT
 CTTCTGTTTCG CCCAGCGAGA TCTCCGCCCC CATCTCCCCC ATTGAGACTG TGCCTGTGAA
 15 GCTGAAGCCTT GGCATGGATG GCCCAAGGT GAAGCAGTGG CCCCTGACTG AGGAGAAGAT
 CAAGGCCCTG GTGGAAATCT GCACTGAGAT GGAGAAGGAG GGCAAAATCT CCAAGATTGG
 CCCCCGAGAAC CCCTACAACA CCCCTGTGTT TGCCATCAAG AAGAAGGACT CCACCAAGTG
 GAGGAAGCTG GTGGACTTCA GGGAGCTGAA CAAGAGGACC CAGGACTTCT GGGAGGTGCA
 GCTGGGCATC CCCCACCCCG CTGGCCTGAA GAAGAAGAAG TCTGTGACTG TGCTGGCTGT
 20 GGGGGATGCC TACTTCTCTG TGCCCCCTGGA TGAGGACTTC AGGAAGTACA CTGCCTTCAC
 CATCCCCCTCC ATCAACAATG AGACCCCTGG CATCAGGTAC CAGTACAATG TGCTGCCCCA
 GGGCTGGAAG GGCTCCCCCTG CCATCTTCCA GTCTCCATG ACCAAGATCC TGGAGCCCTT
 CAGGAAGCAG AACCCTGACA TTGTGATCTA CCAGTACATG GCTGCCCTGT ATGTGGGCTC
 TGACCTGGAG ATTGGGCAGC ACAGGACCAA GATTGAGGAG CTGAGGCAGC ACCTGCTGAG
 25 GTGGGGCCTG ACCACCCCTG ACAAGAAGCA CCAGAAGGAG CCCCCCTTCC TGTGGATGGG
 CTATGAGCTG CACCCCGACA AGTGGACTGT GCAGCCCATT GTGCTGCCCTG AGAAGGACTC
 CTGGACTGTG AATGACATCC AGAAGCTGGT GGGCAAGCTG AACTGGGCCT CCCAAATCTA
 CCCTGGCATC AAGGTGAGGC AGCTGTGCAA GCTGCTGAGG GGCACCAAGG CCCTGACTGA
 GGTGATCCCC CTGACTGAGG AGGCTGAGCT GGAGCTGGCT GAGAACAGGG AGATCCTGAA
 30 GGAGCCTGTG CATGGGGTGT ACTATGACCC CTCCAAGGAC CTGATTGCTG AGATCCAGAA
 GCAGGGCCAG GGCCAGTGGA CCTACCAAAT CTACCAGGAG CCCTTCAAGA ACCTGAAGAC
 TGGCAAGTAT GCCAGGATGA GGGGGGCCCA CACCAATGAT GTGAAGCAGC TGA CTGAGGC
 TGTGCAGAAG ATCACCCTG AGTCCATTGT GATCTGGGGC AAGACCCCCA AGTTCAAGCT
 GCCCATCCAG AAGGAGACCT GGGAGACCTG GTGGACTGAG TACTGGCAGG CCACCTGGAT
 35 CCCTGAGTGG GAGTTTGTGA ACACCCCCC CCTGGTGAAG CTGTGGTACC AGCTGGAGAA
 GGAGCCCATT GTGGGGGCTG AGACCTTCTA TGTGGCTGGG GCTGCCAACA GGGAGACCAA

GCTGGGCAAG GCTGGCTATG TGACCAACAG GGGCAGGCAG AAGGTGGTGA CCCTGACTGA
 CACCACCAAC CAGAAGACTG CCCTCCAGGC CATCTACCTG GCCCTCCAGG ACTCTGGCCT
 GGAGGTGAAC ATTGTGACTG CCTCCCAGTA TGCCCTGGGC ATCATCCAGG CCCAGCCTGA
 TCAGTCTGAG TCTGAGCTGG TGAACCAGAT CATTGAGCAG CTGATCAAGA AGGAGAAGGT
 5 GTACCTGGCC TGGGTGCCTG CCCACAAGGG CATTGGGGGC AATGAGCAGG TGGACAAGCT
 GGTGTCTGCT GGCATCAGGA AGGTGCTGTT CCTGGATGGC ATTGACAAGG CCCAGGATGA
 GCATGAGAAG TACCACTCCA ACTGGAGGGC TATGGCCTCT GACTTCAACC TGCCCCCTGT
 GGTGGCTAAG GAGATTGTGG CCTCCTGTGA CAAGTGCCAG CTGAAGGGGG AGGCCATGCA
 TGGGCAGGTG GACTGCTCCC CTGGCATCTG GCAGCTGGCC TGCACCCACC TGGAGGGCAA
 10 GGTGATCCTG GTGGCTGTGC ATGTGGCCTC CGGCTACATT GAGGCTGAGG TGATCCCTGC
 TGAGACAGGC CAGGAGACTG CCTACTTCCT GCTGAAGCTG GCTGGCAGGT GGCCTGTGAA
 GACCATCCAC ACTGCCAATG GCTCCAACCT CACTGGGGCC ACAGTGAGGG CTGCCTGCTG
 GTGGGCTGGC ATCAAGCAGG AGTTTGGCAT CCCCTACAAC CCCCAGTCCC AGGGGGTGGT
 GGCCTCCATG AACAAGGAGC TGAAGAAGAT CATTGGGCAG GTGAGGGACC AGGCTGAGCA
 15 CCTGAAGACA GCTGTGCAGA TGGCTGTGTT CATCCACAAC TTCAAGAGGA AGGGGGGCAT
 CGGGGGCTAC TCCGCTGGGG AGAGGATTGT GGACATCATT GCCACAGACA TCCAGACCAA
 GGAGCTCCAG AAGCAGATCA CCAAGATCCA GAACCTCAGG GTGTACTACA GGGACTCCAG
 GAACCCCTG TGGAAGGGCC CTGCCAAGCT GCTGTGGAAG GGGGAGGGGG CTGTGGTGAT
 CCAGGACAAC TCTGACATCA AGGTGGTGCC CAGGAGGAAG GCCAAGATCA TCAGGGACTA
 20 TGGCAAGCAG ATGGCTGGGG ATGACTGTGT GGCCTCCAGG CAGGATGAGG ACTAAAGCCC
 GGGCAGATCT (SEQ ID NO:7).

The open reading frame of the tPA-IA-pol construct disclosed as SEQ ID NO:7 contains 875 amino acids, disclosed herein as tPA-IA-Pol and SEQ ID NO:8, as follows:

25 Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly
 Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ala Pro Ile Ser Pro Ile
 Glu Thr Val Pro Val Lys Leu Lys Pro Gly Met Asp Gly Pro Lys Val
 Lys Gln Trp Pro Leu Thr Glu Glu Lys Ile Lys Ala Leu Val Glu Ile
 Cys Thr Glu Met Glu Lys Glu Gly Lys Ile Ser Lys Ile Gly Pro Glu
 30 Asn Pro Tyr Asn Thr Pro Val Phe Ala Ile Lys Lys Lys Asp Ser Thr
 Lys Trp Arg Lys Leu Val Asp Phe Arg Glu Leu Asn Lys Arg Thr Gln
 Asp Phe Trp Glu Val Gln Leu Gly Ile Pro His Pro Ala Gly Leu Lys
 Lys Lys Lys Ser Val Thr Val Leu Ala Val Gly Asp Ala Tyr Phe Ser
 Val Pro Leu Asp Glu Asp Phe Arg Lys Tyr Thr Ala Phe Thr Ile Pro
 35 Ser Ile Asn Asn Glu Thr Pro Gly Ile Arg Tyr Gln Tyr Asn Val Leu
 Pro Gln Gly Trp Lys Gly Ser Pro Ala Ile Phe Gln Ser Ser Met Thr

Lys Ile Leu Glu Pro Phe Arg Lys Gln Asn Pro Asp Ile Val Ile Tyr
 Gln Tyr Met Ala Ala Leu Tyr Val Gly Ser Asp Leu Glu Ile Gly Gln
 His Arg Thr Lys Ile Glu Glu Leu Arg Gln His Leu Leu Arg Trp Gly
 Leu Thr Thr Pro Asp Lys Lys His Gln Lys Glu Pro Pro Phe Leu Trp
 5 Met Gly Tyr Glu Leu His Pro Asp Lys Trp Thr Val Gln Pro Ile Val
 Leu Pro Glu Lys Asp Ser Trp Thr Val Asn Asp Ile Gln Lys Leu Val
 Gly Lys Leu Asn Trp Ala Ser Gln Ile Tyr Pro Gly Ile Lys Val Arg
 Gln Leu Cys Lys Leu Leu Arg Gly Thr Lys Ala Leu Thr Glu Val Ile
 Pro Leu Thr Glu Glu Ala Glu Leu Glu Leu Ala Glu Asn Arg Glu Ile
 10 Leu Lys Glu Pro Val His Gly Val Tyr Tyr Asp Pro Ser Lys Asp Leu
 Ile Ala Glu Ile Gln Lys Gln Gly Gln Gly Gln Trp Thr Tyr Gln Ile
 Tyr Gln Glu Pro Phe Lys Asn Leu Lys Thr Gly Lys Tyr Ala Arg Met
 Arg Gly Ala His Thr Asn Asp Val Lys Gln Leu Thr Glu Ala Val Gln
 Lys Ile Thr Thr Glu Ser Ile Val Ile Trp Gly Lys Thr Pro Lys Phe
 15 Lys Leu Pro Ile Gln Lys Glu Thr Trp Glu Thr Trp Trp Thr Glu Tyr
 Trp Gln Ala Thr Trp Ile Pro Glu Trp Glu Phe Val Asn Thr Pro Pro
 Leu Val Lys Leu Trp Tyr Gln Leu Glu Lys Glu Pro Ile Val Gly Ala
 Glu Thr Phe Tyr Val Ala Gly Ala Ala Asn Arg Glu Thr Lys Leu Gly
 Lys Ala Gly Tyr Val Thr Asn Arg Gly Arg Gln Lys Val Val Thr Leu
 20 Thr Asp Thr Thr Asn Gln Lys Thr Ala Leu Gln Ala Ile Tyr Leu Ala
 Leu Gln Asp Ser Gly Leu Glu Val Asn Ile Val Thr Ala Ser Gln Tyr
 Ala Leu Gly Ile Ile Gln Ala Gln Pro Asp Gln Ser Glu Ser Glu Leu
 Val Asn Gln Ile Ile Glu Gln Leu Ile Lys Lys Glu Lys Val Tyr Leu
 Ala Trp Val Pro Ala His Lys Gly Ile Gly Gly Asn Glu Gln Val Asp
 25 Lys Leu Val Ser Ala Gly Ile Arg Lys Val Leu Phe Leu Asp Gly Ile
 Asp Lys Ala Gln Asp Glu His Glu Lys Tyr His Ser Asn Trp Arg Ala
 Met Ala Ser Asp Phe Asn Leu Pro Pro Val Val Ala Lys Glu Ile Val
 Ala Ser Cys Asp Lys Cys Gln Leu Lys Gly Glu Ala Met His Gly Gln
 Val Asp Cys Ser Pro Gly Ile Trp Gln Leu Ala Cys Thr His Leu Glu
 30 Gly Lys Val Ile Leu Val Ala Val His Val Ala Ser Gly Tyr Ile Glu
 Ala Glu Val Ile Pro Ala Glu Thr Gly Gln Glu Thr Ala Tyr Phe Leu
 Leu Lys Leu Ala Gly Arg Trp Pro Val Lys Thr Ile His Thr Ala Asn
 Gly Ser Asn Phe Thr Gly Ala Thr Val Arg Ala Ala Cys Trp Trp Ala
 Gly Ile Lys Gln Glu Phe Gly Ile Pro Tyr Asn Pro Gln Ser Gln Gly
 35 Val Val Ala Ser Met Asn Lys Glu Leu Lys Lys Ile Ile Gly Gln Val
 Arg Asp Gln Ala Glu His Leu Lys Thr Ala Val Gln Met Ala Val Phe

Ile His Asn Phe Lys Arg Lys Gly Gly Ile Gly Gly Tyr Ser Ala Gly
 Glu Arg Ile Val Asp Ile Ile Ala Thr Asp Ile Gln Thr Lys Glu Leu
 Gln Lys Gln Ile Thr Lys Ile Gln Asn Phe Arg Val Tyr Tyr Arg Asp
 Ser Arg Asn Pro Leu Trp Lys Gly Pro Ala Lys Leu Leu Trp Lys Gly
 5 Glu Gly Ala Val Val Ile Gln Asp Asn Ser Asp Ile Lys Val Val Pro
 Arg Arg Lys Ala Lys Ile Ile Arg Asp Tyr Gly Lys Gln Met Ala Gly
 Asp Asp Cys Val Ala Ser Arg Gln Asp Glu Asp (SEQ ID NO:8).

EXAMPLE 18

10 CODON OPTIMIZED HIV-1 NEF AND CODON OPTIMIZED HIV-1 NEF MODIFICATIONS

Codon optimized version of HIV-1 Nef and HIV-1 Nef modifications are essentially as described in U.S. Application Serial No. 09/738,782, filed December 15, 2000 and PCT International Application PCT/US00/34162, also filed
 15 December 15, 2000, both documents which are hereby incorporated by reference. As disclosed within the above-mentioned documents, particular embodiments of codon optimized Nef and Nef modifications relate to a DNA molecule encoding HIV-1 Nef from the HIV-1 jfrr isolate wherein the codons are optimized for expression in a mammalian system such as a human. The DNA molecule which encodes this protein
 20 is disclosed herein as SEQ ID NO:9, while the expressed open reading frame is disclosed herein as SEQ ID NO:10. Another embodiment of Nef-based coding regions for use in the adenoviral vectors of the present invention comprise a codon optimized DNA molecule encoding a protein containing the human plasminogen activator (tpa) leader peptide fused with the NH₂-terminus of the HIV-1 Nef
 25 polypeptide. The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:11, while the expressed open reading frame is disclosed herein as SEQ ID NO:12. Another modified Nef optimized coding region relates to a DNA molecule encoding optimized HIV-1 Nef wherein the open reading frame codes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and
 30 substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175, herein described as opt nef (G2A, LLAA). The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:13, while the expressed open reading frame is disclosed herein as SEQ ID NO:14. An additional embodiment relates to a DNA molecule encoding optimized HIV-1 Nef wherein the amino terminal myristylation
 35 site and dileucine motif have been deleted, as well as comprising a tPA leader peptide. This DNA molecule, opt tpanef (LLAA), comprises an open reading frame which

encodes a Nef protein containing a tPA leader sequence fused to amino acid residue 6-216 of HIV-1 Nef (jfrl), wherein Leu-174 and Leu-175 are substituted with Ala-174 and Ala-175, herein referred to as opt tpanef (LLAA) is disclosed herein as SEQ ID NO:15, while the expressed open reading frame is disclosed herein as SEQ ID NO:16.

5 As disclosed in the above-identified documents (U.S. Application Serial No. 09/738,782 and PCT International Application PCT/US00/34162) and reiterated herein, the following nef-based nucleotide and amino acid sequences which comprise the respective open reading frame are as follows:

1. The nucleotide sequence of the codon optimized version of HIV-1 jfrl
10 nef gene is disclosed herein as SEQ ID NO:9, as shown herein:

GATCTGCCAC CATGGGCGGC AAGTGGTCCA AGAGGTCCGT GCCCGGCTGG TCCACCGTGA
GGGAGAGGAT GAGGAGGGCC GAGCCCGCCG CCGACAGGGT GAGGAGGACC GAGCCCGCCG
CCGTGGGCGT GGGCGCCGTG TCCAGGGACC TGGAGAAGCA CGGCGCCATC ACCTCCTCCA
ACACCGCCGC CACCAACGCC GACTGCGCCT GGCTGGAGGC CCAGGAGGAC GAGGAGGTGG
15 GCTTCCCCGT GAGGCCCCAG GTGCCCTTGA GGCCCATGAC CTACAAGGGC GCCGTGGACC
TGTTCCACTT CTTGAAGGAG AAGGGCGGCC TGGAGGGCCT GATCCACTCC CAGAAGAGGC
AGGACATCCT GGACCTGTGG GTGTACCACA CCCAGGGCTA CTTCCCCGAC TGGCAGAACT
ACACCCCCGG CCCCAGGCATC AGGTTCCCCC TGACCTTCGG CTGGTGCTTC AAGCTGGTGC
CCGTGGAGCC CGAGAAGGTG GAGGAGGCCA ACGAGGGCGA GAACAAGTGC CTGCTGCACC
20 CCATGTCCCA GCACGGCATC GAGGACCCCG AGAAGGAGGT GCTGGAGTGG AGGTTGCACT
CCAAGCTGGC CTTCCACCAC GTGGCCAGGG AGCTGCACCC CGAGTACTAC AAGGACTGCT
AAAGCCCGGG C (SEQ ID NO:9).

Preferred codon usage is as follows: Met (ATG), Gly (GGC), Lys (AAG),
Trp (TGG), Ser (TCC), Arg (AGG), Val (GTG), Pro (CCC), Thr (ACC), Glu (GAG);
25 Leu (CTG), His (CAC), Ile (ATC), Asn (AAC), Cys (TGC), Ala (GCC), Gln (CAG),
Phe (TTC) and Tyr (TAC). For an additional discussion relating to mammalian
(human) codon optimization, see WO 97/31115 (PCT/US97/02294), which is hereby
incorporated by reference. See also Figure 19A-B for a comparison of wild type vs.
codon optimized nucleotides comprising the open reading frame of HIV-Nef.

30 The open reading frame for SEQ ID NO:9 above comprises an initiating
methionine-residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides
660-662. The open reading frame of SEQ ID NO:9 provides for a 216 amino acid
HIV-1 Nef protein expressed through utilization of a codon optimized DNA vaccine
vector. The 216 amino acid HIV-1 Nef (jfrl) protein is disclosed herein as SEQ ID
35 NO:10, and as follows:

Met Gly Gly Lys Trp Ser Lys Arg Ser Val Pro Gly Trp Ser Thr Val

Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala Asp Arg Val Arg Arg
 Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val Ser Arg Asp Leu Glu
 Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala Ala Thr Asn Ala Asp
 Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu Val Gly Phe Pro Val
 5 Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr Lys Gly Ala Val Asp
 Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu Glu Gly Leu Ile His
 Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp Val Tyr His Thr Gln
 Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro Gly Pro Gly Ile Arg
 Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu Val Pro Val Glu Pro
 10 Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn Asn Cys Leu Leu His
 Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu Lys Glu Val Leu Glu
 Trp Arg Phe Asp Ser Lys Leu Ala Phe His His Val Ala Arg Glu Leu
 His Pro Glu Tyr Tyr Lys Asp Cys (SEQ ID NO:10).

HIV-1 Nef is a 216 amino acid cytosolic protein which associates with the
 15 inner surface of the host cell plasma membrane through myristylation of Gly-2
 (Franchini et al., 1986, *Virology* 155: 593-599). While not all possible Nef functions
 have been elucidated, it has become clear that correct trafficking of Nef to the inner
 plasma membrane promotes viral replication by altering the host intracellular
 environment to facilitate the early phase of the HIV-1 life cycle and by increasing the
 20 infectivity of progeny viral particles. In one aspect of the invention regarding
 codon-optimized, protein-modified polypeptides, the nef-encoding region of the
 adenovirus vector of the present invention is modified to contain a nucleotide
 sequence which encodes a heterologous leader peptide such that the amino terminal
 region of the expressed protein will contain the leader peptide. The diversity of
 25 function that typifies eukaryotic cells depends upon the structural differentiation of
 their membrane boundaries. To generate and maintain these structures, proteins must
 be transported from their site of synthesis in the endoplasmic reticulum to
 predetermined destinations throughout the cell. This requires that the trafficking
 proteins display sorting signals that are recognized by the molecular machinery
 30 responsible for route selection located at the access points to the main trafficking
 pathways. Sorting decisions for most proteins need to be made only once as they
 traverse their biosynthetic pathways since their final destination, the cellular location
 at which they perform their function, becomes their permanent residence.
 Maintenance of intracellular integrity depends in part on the selective sorting and
 35 accurate transport of proteins to their correct destinations. Defined sequence motifs
 exist in proteins which can act as 'address labels'. A number of sorting signals have

been found associated with the cytoplasmic domains of membrane proteins. An effective induction of CTL responses often required sustained, high level endogenous expression of an antigen. As membrane-association via myristylation is an essential requirement for most of Nef's function, mutants lacking myristylation, by glycine-to-
5 alanine change, change of the dileucine motif and/or by substitution with a tpa leader sequence as described herein, will be functionally defective, and therefore will have improved safety profile compared to wild-type Nef for use as an HIV-1 vaccine component.

In another embodiment of this portion of the invention, either the DNA vector
10 or the HIV-1 nef nucleotide sequence is modified to include the human tissue-specific plasminogen activator (tPA) leader. As shown in Figure 16A-B, a DNA vector may be modified by known recombinant DNA methodology to contain a leader signal peptide of interest, such that downstream cloning of the modified HIV-1 protein of interest results in a nucleotide sequence which encodes a modified HIV-1 tPA/Nef
15 protein. In the alternative, as noted above, insertion of a nucleotide sequence which encodes a leader peptide may be inserted into a DNA vector housing the open reading frame for the Nef protein of interest. Regardless of the cloning strategy, the end result is a polynucleotide vaccine which comprises vector components for effective gene expression in conjunction with nucleotide sequences which encode a modified HIV-1
20 Nef protein of interest, including but not limited to a HIV-1 Nef protein which contains a leader peptide. The amino acid sequence of the human tPA leader utilized herein is as follows: MDAMKRGLCCVLLLCGAVFVSPSEISS (SEQ ID NO:17).

It has been shown that myristylation of Gly-2 in conjunction with a dileucine motif in the carboxy region of the protein is essential for Nef-induced down
25 regulation of CD4 (Aiken et al., 1994, *Cell* 76: 853-864) via endocytosis. It has also been shown that Nef expression promotes down regulation of MHC I (Schwartz et al., 1996, *Nature Medicine* 2(3): 338-342) via endocytosis. The present invention relates in part to DNA vaccines which encode modified Nef proteins altered in trafficking and/or functional properties. The modifications introduced into the adenoviral vector
30 HIV vaccines of the present invention include but are not limited to additions, deletions or substitutions to the nef open reading frame which results in the expression of a modified Nef protein which includes an amino terminal leader peptide, modification or deletion of the amino terminal myristylation site, and modification or deletion of the dileucine motif within the Nef protein and which alter
35 function within the infected host cell. Therefore, a central theme of the DNA molecules and recombinant adenoviral HIV vaccines of the present invention is (1)

host administration and intracellular delivery of a codon optimized nef-based adenoviral HIV vaccine; (2) expression of a modified Nef protein which is immunogenic in terms of eliciting both CTL and Th responses; and, (3) inhibiting or at least altering known early viral functions of Nef which have been shown to promote HIV-1 replication and load within an infected host. Therefore, the nef coding region may be altered, resulting in a DNA vaccine which expresses a modified Nef protein wherein the amino terminal Gly-2 myristylation residue is either deleted or modified to express alternate amino acid residues. Also, the nef coding region may be altered so as to result in a DNA vaccine which expresses a modified Nef protein wherein the dileucine motif is either deleted or modified to express alternate amino acid residues. In addition, the adenoviral vector HIV vaccines of the present invention also relate to an isolated DNA molecule, regardless of codon usage, which expresses a wild type or modified Nef protein as described herein, including but not limited to modified Nef proteins which comprise a deletion or substitution of Gly 2, a deletion or substitution of Leu 174 and Leu 175 and/or inclusion of a leader sequence.

Therefore, specific Nef-based constructs further include the following, as exemplification's and not limitations. For example, the present invention relates to an adenoviral vector vaccine which encodes modified forms of HIV-1, an open reading frame which encodes a Nef protein which comprises a tPA leader sequence fused to amino acid residue 6-216 of HIV-1 Nef (jfr1) is referred to herein as opt tpanef. The nucleotide sequence comprising the open reading frame of opt tpanef is disclosed herein as SEQ ID NO:11, as shown below:

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CATGGATGCA ATGAAGAGAG GGCTCTGCTG TGTGCTGCTG CTGTGTGGAG CAGTCTTCGT
TTGCCCCAGC GAGATCTCCT CCAAGAGGTC CGTGCCCGGC TGGTCCACCG TGAGGGAGAG
GATGAGGAGG GCCGAGCCCG CCGCCGACAG GGTGAGGAGG ACCGAGCCCG CCGCCGTGGG
CGTGGGCGCC GTGTCCAGGG ACCTGGAGAA GCACGGCGCC ATCACCTCCT CCAACACCGC
CGCCACCAAC GCCGACTGCG CCTGGCTGGA GGCCCAGGAG GACGAGGAGG TGGGCTTCCC
CGTGAGGCCC CAGGTGCCCC TGAGGCCCAT GACCTACAAG GGCGCCGTGG ACCTGTCCCCA
CTTCTGAAG GAGAAGGGCG GCCTGGAGGG CCTGATCCAC TCCCAGAAGA GGCAGGACAT
CCTGGACCTG TGGGTGTACC ACACCCAGGG CTACTTCCCC GACTGGCAGA ACTACACCCC
CGGCCCCGGC ATCAGGTTCC CCCTGACCTT CGGCTGGTGC TTCAAGCTGG TGGCCGTGGA
GCCCAGAGAAG GTGGAGGAGG CCAACGAGGG CGAGAACAAC TGCCTGCTGC ACCCCATGTC
CCAGCACGGC ATCGAGGACC CCGAGAAGGA GGTGCTGGAG TGGAGGTTTC ACTCCAAGCT
GGCCTTCCAC CACGTGGCCA GGGAGCTGCA CCCCAGGTAC TACAAGGACT GCTAAAGCC
(SEQ ID NO:11).

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The open reading frame for SEQ ID NO:11 comprises an initiating methionine

residue at nucleotides 2-4 and a "TAA" stop codon from nucleotides 713-715. The open reading frame of SEQ ID NO:3 provides for a 237 amino acid HIV-1 Nef protein which comprises a tPA leader sequence fused to amino acids 6-216 of HIV-1 Nef, including the dileucine motif at amino acid residues 174 and 175. This 237 amino acid tPA/Nef (jfrl) fusion protein is disclosed herein as SEQ ID NO:12, and is shown as follows:

Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly
 Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ser Lys Arg Ser Val Pro
 Gly Trp Ser Thr Val Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala
 10 Asp Arg Val Arg Arg Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val
 Ser Arg Asp Leu Glu Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala
 Ala Thr Asn Ala Asp Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu
 Val Gly Phe Pro Val Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr
 Lys Gly Ala Val Asp Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu
 15 Glu Gly Leu Ile His Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp
 Val Tyr His Thr Gln Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro
 Gly Pro Gly Ile Arg Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu
 Val Pro Val Glu Pro Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn
 Asn Cys Leu Leu His Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu
 20 Lys Glu Val Leu Glu Trp Arg Phe Asp Ser Lys Leu Ala Phe His His
 Val Ala Arg Glu Leu His Pro Glu Tyr Tyr Lys Asp Cys (SEQ ID NO:12).

Therefore, this exemplified Nef protein, Opt tPA-Nef, contains both a tPA leader sequence as well as deleting the myristylation site of Gly-2A DNA molecule encoding HIV-1 Nef from the HIV-1 jfrl isolate wherein the codons are optimized for expression in a mammalian system such as a human.

In another specific embodiment of the present invention, a DNA molecule is disclosed which encodes optimized HIV-1 Nef wherein the open reading frame of a recombinant adenoviral HIV vaccine encodes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175. This open reading frame is herein described as opt nef (G2A,LLAA) and is disclosed as SEQ ID NO:13, which comprises an initiating methionine residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides 660-662. The nucleotide sequence of this codon optimized version of HIV-1 jfrl nef gene with the above mentioned modifications is disclosed herein as SEQ ID NO:13, as follows:

GATCTGCCAC CATGGCCGGC AAGTGGTCCA AGAGGTCCGT GCCCGGCTGG TCCACCGTGA
 GGGAGAGGAT GAGGAGGGCC GAGCCCGCCG CCGACAGGGT GAGGAGGACC GAGCCCGCCG
 CCGTGGGCGT GGGCGCCGTG TCCAGGGACC TGGAGAAGCA CGGCGCCATC ACCTCCTCCA
 ACACCGCCGC CACCAACGCC GACTGCGCCT GGCTGGAGGC CCAGGAGGAC GAGGAGGTGG
 5 GCTTCCCCGT GAGGCCCCAG GTGCCCCCTGA GGCCCATGAC CTACAAGGGC GCCGTGGACC
 TGTCCCACTT CCTGAAGGAG AAGGGCGGCC TGGAGGGCCT GATCCACTCC CAGAAGAGGC
 AGGACATCCT GGACCTGTGG GTGTACCACA CCCAGGGCTA CTTCCCCGAC TGGCAGAACT
 ACACCCCCCG CCCCGGCATC AGGTTCCTCC TGACCTTCGG CTGGTGCTTC AAGCTGGTGC
 CCGTGGAGCC CGAGAAGGTG GAGGAGGCCA ACGAGGGCGA GAACAACTGC GCCGCCACC
 10 CCATGTCCCA GCACGGCATC GAGGACCCCG AGAAGGAGGT GCTGGAGTGG AGGTTCTGACT
 CCAAGCTGGC CTTCCACCAC GTGGCCAGGG AGCTGCACCC CGAGTACTAC AAGGACTGCT
 AAAGCCCGGG C (SEQ ID NO:13).

The open reading frame of SEQ ID NO:13 encodes Nef (G2A,LLAA), disclosed herein as SEQ ID NO:14, as follows:

15 Met Ala Gly Lys Trp Ser Lys Arg Ser Val Pro Gly Trp Ser Thr Val
 Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala Asp Arg Val Arg Arg
 Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val Ser Arg Asp Leu Glu
 Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala Ala Thr Asn Ala Asp
 Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu Val Gly Phe Pro Val
 20 Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr Lys Gly Ala Val Asp
 Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu Glu Gly Leu Ile His
 Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp Val Tyr His Thr Gln
 Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro Gly Pro Gly Ile Arg
 Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu Val Pro Val Glu Pro
 25 Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn Asn Cys Ala Ala His
 Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu Lys Glu Val Leu Glu
 Trp Arg Phe Asp Ser Lys Leu Ala Phe His His Val Ala Arg Glu Leu
 His Pro Glu Tyr Tyr Lys Asp Cys Ser (SEQ ID NO:14).

An additional embodiment of the present invention relates to another DNA
 30 molecule encoding optimized HIV-1 Nef wherein the amino terminal myristylation
 site and dileucine motif have been deleted, as well as comprising a tPA leader peptide.
 This DNA molecule, opt tpanef (LLAA) comprises an open reading frame which
 encodes a Nef protein containing a tPA leader sequence fused to amino acid residue
 6-216 of HIV-1 Nef (jfr1), wherein Leu-174 and Leu-175 are substituted with Ala-174
 35 and Ala-175 (Ala-195 and Ala-196 in this tPA-based fusion protein). The nucleotide

sequence comprising the open reading frame of opt tpanef (LLAA) is disclosed herein as SEQ ID NO:15, as shown below:

CATGGATGCA ATGAAGAGAG GGCTCTGCTG TGTGCTGCTG CTGTGTGGAG CAGTCTTCGT
 TTCGCCCAGC GAGATCTCCT CCAAGAGGTC CGTGCCCGGC TGGTCCACCG TGAGGGAGAG
 5 GATGAGGAGG GCCGAGCCCG CCGCCGACAG GGTGAGGAGG ACCGAGCCCG CCGCCGTGGG
 CGTGGGCGCC GTGTCCAGGG ACCTGGAGAA GCACGGCGCC ATCACCTCCT CCAACACCGC
 CGCCACCAAC GCCGACTGCG CCTGGCTGGA GGCCAGGAG GACGAGGAGG TGGGCTTCCC
 CGTGAGGCCC CAGGTGCCCC TGAGGCCCAT GACCTACAAG GGCGCCGTGG ACCTGTCCCA
 CTTCTGAAG GAGAAGGGCG GCCTGGAGGG CCTGATCCAC TCCCAGAAGA GGCAGGACAT
 10 CCTGGACCTG TGGGTGTACC ACACCCAGGG CTACTTCCCC GACTGGCAGA ACTACACCCC
 CGGCCCCGGC ATCAGGTTCC CCCTGACCTT CGGCTGGTGC TTCAAGCTGG TGCCCGTGGA
 GCCCCGAGAAG GTGGAGGAGG CCAACGAGGG CGAGAACAAC TGCGCCGCC ACCCCATGTC
 CCAGCACGGC ATCGAGGACC CCGAGAAGGA GGTGCTGGAG TGGAGGTTTCG ACTCCAAGCT
 GGCTTCCAC CACGTGGCCA GGGAGCTGCA CCCCAGTAC TACAAGGACT GCTAAAGCCC
 15 (SEQ ID NO:15).

The open reading frame of SEQ ID NO:7 encoding tPA-Nef (LLAA), disclosed herein as SEQ ID NO:16, is as follows:

Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly
 Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ser Lys Arg Ser Val Pro
 20 Gly Trp Ser Thr Val Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala
 Asp Arg Val Arg Arg Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val
 Ser Arg Asp Leu Glu Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala
 Ala Thr Asn Ala Asp Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu
 Val Gly Phe Pro Val Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr
 25 Lys Gly Ala Val Asp Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu
 Glu Gly Leu Ile His Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp
 Val Tyr His Thr Gln Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro
 Gly Pro Gly Ile Arg Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu
 Val Pro Val Glu Pro Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn
 30 Asn Cys Ala Ala His Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu
 Lys Glu Val Leu Glu Trp Arg Phe Asp Ser Lys Leu Ala Phe His His
 Val Ala Arg Glu Leu His Pro Glu Tyr Tyr Lys Asp Cys (SEQ ID NO:16).

An adenoviral vector of the present invention may comprise a DNA sequence,
 regardless of codon usage, which expresses a wild type or modified Nef protein as
 35 described herein, including but not limited to modified Nef proteins which comprise a
 deletion or substitution of Gly 2, a deletion or substitution of Leu 174 and Leu 175

and/or inclusion of a leader sequence. Therefore, partial or fully codon optimized DNA vaccine expression vector constructs are preferred since such constructs should result in increased host expression. However, it is within the scope of the present invention to utilize "non-codon optimized" versions of the constructs disclosed herein, especially modified versions of HIV Nef which are shown to promote a substantial cellular immune response subsequent to host administration.

Figure 20A-C show nucleotide sequences at junctions between nef coding sequence and plasmid backbone of nef expression vectors V1Jns/nef (Figure 20A), V1Jns/nef(G2A,LLAA) (Figure 20B), V1Jns/tpanef (Figure 20C) and V1Jns/tpanef(LLAA) (Figure 20C, also). 5' and 3' flanking sequences of codon optimized nef or codon optimized nef mutant genes are indicated by bold/italic letters; nef and nef mutant coding sequences are indicated by plain letters. Also indicated (as underlined) are the restriction endonuclease sites involved in construction of respective nef expression vectors. V1Jns/tpanef and V1Jns/tpanef(LLAA) have identical sequences at the junctions.

Figure 21 shows a schematic presentation of nef and nef derivatives. Amino acid residues involved in Nef derivatives are presented. Glycine 2 and Leucine 174 and 175 are the sites involved in myristylation and dileucine motif, respectively.

EXAMPLE 19

MRKAd5Pol Construction and Virus Rescue

Construction of vector: shuttle plasmid and pre-adenovirus plasmid - Key steps performed in the construction of the vectors, including the pre-adenovirus plasmid denoted MRKAd5pol, is depicted in Figure 22. Briefly, the adenoviral shuttle vector for the full-length inactivated HIV-1 pol gene is as follows. The vector MRKpdelE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.) is a derivative of the shuttle vector used in the construction of the MRKAd5gag adenoviral pre-plasmid. The vector contains an expression cassette with the hCMV promoter (no intronA) and the bovine growth hormone polyadenylation signal. The expression unit has been inserted into the shuttle vector such that insertion of the gene of choice at a unique *Bgl*II site will ensure the direction of transcription of the transgene will be Ad5 E1 parallel when inserted into the MRKpAd5(E1-/E3+)ClaI (or MRKpAdHVE3) pre-plasmid. The vector, similar to the original shuttle vector contains the *Pac*I site, extension to the packaging signal region, and extension to the pIX gene. The synthetic full-length codon-optimized HIV-1 pol gene was isolated directly from the plasmid pV1Jns-HIV-pol-inact(opt). Digestion of this plasmid with *Bgl*II releases the pol

gene intact (comprising a codon optimized IA pol sequence as disclosed in SEQ ID NO:3). The pol fragment was gel purified and ligated into the MRKpdelE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.) shuttle vector at the *Bgl*III site. The clones were checked for the correct orientation of the gene by using
 5 restriction enzymes *Dra*III/*Not*I. A positive clone was isolated and named MRKpdel+hCMVmin+FL-pol+bGHpA(s). The genetic structure of this plasmid was verified by PCR, restriction enzyme and DNA sequencing. The pre-adenovirus plasmid was constructed as follows. Shuttle plasmid MRKpdel+hCMVmin+FL-pol+bGHpA(S) was digested with restriction enzymes *Pac*I and *Bst*1107 I (or its
 10 isoschizomer, *Bst*Z107 I) and then co-transformed into *E. coli* strain BJ5183 with linearized (*Cla*I digested) adenoviral backbone plasmid, MRKpAd(E1-/E3+)ClaI. The resulting pre-plasmid originally named MRKpAd+hCMVmin+FL-pol+bGHpA(S)E3+ is now referred to as "pMRKAd5pol". The genetic structure of the resulting pMRKAd5pol was verified by PCR, restriction enzyme and DNA
 15 sequence analysis. The vectors were transformed into competent *E. coli* XL-1 Blue for preparative production. The recovered plasmid was verified by restriction enzyme digestion and DNA sequence analysis, and by expression of the pol transgene in transient transfection cell culture. The complete nucleotide sequence of this pMRKAd5HIV-1pol adenoviral vector is shown in Figure 26 A-AO.

20 *Generation of research-grade recombinant adenovirus* - The pre-adenovirus plasmid, pMRKAd5pol, was rescued as infectious virions in PER.C6[®] adherent monolayer cell culture. To rescue infectious virus, 12 µg of pMRKAd5pol was digested with restriction enzyme *Pac*I (New England Biolabs) and 3.3 µg was transfected per 6 cm dish of PER.C6[®] cells using the calcium phosphate co-
 25 precipitation technique (Cell Pfect Transfection Kit, Amersham Pharmacia Biotech Inc.). *Pac*I digestion releases the viral genome from plasmid sequences allowing viral replication to occur after entry into PER.C6[®] cells. Infected cells and media were harvested 6 -10 days post-transfection, after complete viral cytopathic effect (CPE) was observed. Infected cells and media were stored at ≤ -60°C. This pol containing
 30 recombinant adenovirus is referred to herein as "MRKAd5pol". This recombinant adenovirus expresses an inactivated HIV-1 Pol protein as shown in SEQ ID NO:6.

EXAMPLE 20

MRKAd5Nef Construction and Virus Rescue

35 *Construction of vector: shuttle plasmid and pre-adenovirus plasmid* - Key steps performed in the construction of the vectors, including the pre-adenovirus

plasmid denoted MRKAd5nef, is depicted in Figure 23. Briefly, as shown in Example 19 above, the vector MRKpdeIE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.) is the shuttle vector used in the construction of the MRKAd5gag adenoviral pre-plasmid. It has been modified to contain the *Pac*1 site, extension to the packaging signal region, and extension to the pIX gene. It contains an expression cassette with the hCMV promoter (no intronA) and the bovine growth hormone polyadenylation signal. The expression unit has been inserted into the shuttle vector such that insertion of the gene of choice at a unique *Bgl*11 site will ensure the direction of transcription of the transgene will be Ad5 E1 parallel when inserted into the MRKpAd5(E1-/E3+)Cla1 pre-plasmid. The synthetic full-length codon-optimized HIV-1 nef gene was isolated directly from the plasmid pV1Jns/nef (G2A,LLAA). Digestion of this plasmid with *Bgl*11 releases the pol gene intact, which comprises the nucleotide sequence as disclosed in SEQ ID NO:13. The nef fragment was gel purified and ligated into the MRKpdeIE1+CMVmin+BGHpA(str.) shuttle vector at the *Bgl*11 site. The clones were checked for correction orientation of the gene by using restriction enzyme *Sca*1. A positive clone was isolated and named MRKpdeIE1hCMVminFL-nefBGHpA(s). The genetic structure of this plasmid was verified by PCR, restriction enzyme and DNA sequencing. The pre-adenovirus plasmid was constructed as follows. Shuttle plasmid MRKpdeIE1hCMVminFL-nefBGHpA(s) was digested with restriction enzymes *Pac*1 and *Bst*1107 I (or its isoschizomer, *Bst*Z107 I) and then co-transformed into *E. coli* strain BJ5183 with linearized (*Cla*1 digested) adenoviral backbone plasmid, MRKpAd(E1/E3+)Cla1. The resulting pre-plasmid originally named MRKpdeIE1hCMVminFL-nefBGHpA(s) is now referred to as "pMRKAd5nef". The genetic structure of the resulting pMRKAd5nef was verified by PCR, restriction enzyme and DNA sequence analysis. The vectors were transformed into competent *E. coli* XL-1 Blue for preparative production. The recovered plasmid was verified by restriction enzyme digestion and DNA sequence analysis, and by expression of the nef transgene in transient transfection cell culture. The complete nucleotide sequence of this pMRKAd5HIV-1nef adenoviral vector is shown in Figure 27A-AM.

Generation of research-grade recombinant adenovirus - The pre-adenovirus plasmid, pMRKAd5nef, was rescued as infectious virions in PER.C6[®] adherent monolayer cell culture. To rescue infectious virus, 12 µg of pMRKAdnef was digested with restriction enzyme *Pac*1 (New England Biolabs) and 3.3 µg was transfected per 6 cm dish of PER.C6[®] cells using the calcium phosphate co-precipitation technique (Cell Pfect Transfection Kit, Amersham Pharmacia Biotech

Inc.). *Pac1* digestion releases the viral genome from plasmid sequences allowing viral replication to occur after entry into PER.C6[®] cells. Infected cells and media were harvested 6 -10 days post-transfection, after complete viral cytopathic effect (CPE) was observed. Infected cells and media were stored at $\leq -60^{\circ}\text{C}$. This nef containing recombinant adenovirus is now referred to as "MRKAd5nef".

EXAMPLE 21

Construction of Murine CMV Promoter Containing Shuttle Vectors for Inactivated Pol and Nef/G2A,LLAA

10 The murine CMV (mCMV) was amplified from the plasmid pMH4 (supplied by Frank Graham, McMaster University) using the primer set: mCMV (*Not* I) Forward: 5'-ATA AGA ATG CGG CCG CCA TAT ACT GAG TCA TTA GG-3' (SEQ ID NO: 20); mCMV (*Bgl* II) Reverse: 5'-AAG GAA GAT CTA CCG ACG CTG GTC GCG CCT C-3' (SEQ ID NO:21). The underlined nucleotides represent the *Not* I and the *Bgl* II sites respectively for each primer. This PCR amplicon was used for the construction of the mCMV shuttle vector containing the transgene in the E1 parallel orientation. The hCMV promoter was removed from the original shuttle vector (containing the hCMV-gag-bGHpA transgene in the E1 parallel orientation) by digestion with *Not* I and *Bgl* II. The mCMV promoter (*Not* I/*Bgl* II digested PCR product) was inserted into the shuttle vector in a directional manner. The shuttle vector was then digested with *Bgl* II and the gag reporter gene (*Bgl* II fragment) was re-inserted back into the shuttle vector. Several clones were screened for correct orientation of the reporter gene. For the construction of the mCMV-gag in the E1 antiparallel orientation, the mCMV promoter was amplified from the plasmid pMH4 using the following primer set: mCMV (*Asc* I) Forward: 5'- ATA AGA ATG GCG CGC CAT ATA CTG AGT CAT TAG G (SEQ ID NO:22); mCMV (*Bgl* II) Reverse: 5' AAG GAA GAT CTA CCG ACG CTG GTC GCG CCT C (SEQ ID NO:23). The underlined nucleotides represent the *Asc* I and *Bgl* II sites, respectively for each primer. The shuttle vector containing the hCMV-gag transgene in the E1 antiparallel orientation was digested with *Asc* I and *Bgl* II to remove the hCMV-gag portion of the transgene. The mCMV promoter (*Asc* I/*Bgl* II digested PCR product) was inserted into the shuttle vector in a directional manner. The vector was then digested with *Bgl* II and the gag reporter gene (*Bgl* II fragment) was re-inserted. Several clones were screened for correct orientation of the reporter gene. For each of the full length IA pol and full length nef/G2A,LLAA genes, cloning was performed using the unique

Bgl II site within the mCMV-bGHpA shuttle vector. The pol and nef genes were excised from their respective pV1Jns plasmids by *Bgl* II digestion.

EXAMPLE 22

5 Construction of mCMV Full Length Inactivated Pol and Full Length nef/G2A.LLAA Adenovectors

Each of these transgenes of Example 21 were inserted into the modified shuttle vector in both the E1 parallel and E1 anti-parallel orientations. *Pac*I and *Bst*Z110I digestion of each shuttle vector was performed and each specific transgene
10 fragment containing the flanking Ad5 sequences was isolated and co-transformed with *Cla*I digested MRKpAd5(E3+) or MRKpAd5(E3-) adenovector plasmids via bacterial homologous recombination in BJ5183 *E. coli* cells. Recombinant pre-plasmid adenovectors containing the various transgenes in both the E3- and E3+ versions (and in the E1 parallel and E1 antiparallel orientations) were subsequently
15 prepared in large scale following transformation into XL-1 Blue *E. coli* cells and analyzed by restriction analysis and sequencing.

EXAMPLE 23

Construction of hCMV-tpa-nef (LLAA) Adenovector

20 The tpa-nef gene was amplified out from GMP grade pV1Jns-tpanef (LLAA) vector using the primer sets: Tpanef (*Bam*HI) F 5'-ATT GGA TCC ATG GAT GCA ATG AAG AGA GGG (SEQ ID 24); Tpanef (*Bam*HI) R 5'-ATA GGA TCC TTA GCA GTC CTT GTA GTA CTC G (SEQ ID NO:25). The resulting PCR product was digested with *Bam*HI, gel purified and cloned into the *Bgl* II site of MRKAd5CMV-bGHpA shuttle vector (*Bgl* II digested and calf intestinal phosphatase treated).
25 Clones containing the tpanef (LLAA) gene (see SEQ ID NO:15 for complet coding region) in the correct orientation with respect to the hCMV promoter were selected following *Sca*I digestion. The resulting MRKAd5tpanef shuttle vector was digested with *Pac*I and *Bst*Z110I and cloned into the E3+ MRKAd5 adenovector via bacterial
30 homologous recombination techniques.

EXAMPLE 24

Immunogenicity of MRKAd5pol and MRKAd5nef Vaccine

Materials and Methods - Rodent Immunization - Groups of N=10 BALB/c
35 mice were immunized i.m. with the following vectors: (1) MRKAd5hCMV-IApol (E3+) at either 10^7 vp and 10^9 vp; and (2) MRKAd5hCMV-IApol (E3-) at either

10⁷ vp and 10⁹ vp. At 7 weeks post dose, 5 of the 10 mice per cohort were boosted with the same vector and dose they initially received. At 3 weeks post the second dose, sera and spleens were collected from all the animals for RT ELISA and IFN γ ELISpot analyses, respectively. For all rodent immunizations, the Ad5 vectors were
5 diluted in 5 mM Tris, 5% sucrose, 75 mM NaCl, 1 mM MgCl₂, 0.005% polysorbate 80, pH 8.0. The total dose was injected to both quadricep muscles in 50 μ L aliquots using a 0.3-mL insulin syringe with 28-1/2G needles (Becton-Dickinson, Franklin Lakes, NJ).

Groups of N=10 C57/BL6 mice were immunized i.m. with the following
10 vectors: (1) MRKAd5hCMV-nef(G2A,LLAA) (E3+) at either 10⁷ vp and 10⁹ vp; (2) MRKAd5mCMV-nef(G2A,LLAA) (E3+) at either 10⁷ vp and 10⁹ vp; and (3) MRKAd5mCMV-tpanef(LLAA) (E3+) at either 10⁷ vp and 10⁹ vp. At 7 weeks post dose, 5 of the 10 mice per cohort were boosted with the same vector and dose they initially received. At 3 weeks post the second dose, sera and spleens were
15 collected from all the animals for RT ELISA and IFN γ ELISpot analyses, respectively.

Non-human Primate immunization - Cohorts of 3 rhesus macaques (2-3 kg) were vaccinated with the following Ad vectors: (1) MRKAd5hCMV-IApol (E3+) at either 10⁹ vp and 10¹¹ vp dose; and (2) MRKAd5hCMV-IApol (E3-) at either
20 10⁹ vp and 10¹¹ vp; (3) MRKAd5hCMV-nef(G2A,LLAA) (E3+) at either 10⁹ vp and 10¹¹ vp; and (4) MRKAd5mCMV-nef(G2A,LLAA) (E3+) at either 10⁹ vp and 10¹¹ vp. The vaccine was administered to chemically restrained monkeys (10 mg/kg ketamine) by needle injection of two 0.5 mL aliquots of the Ad vectors (in 5 mM Tris, 5% sucrose, 75 mM NaCl, 1 mM MgCl₂, 0.005% polysorbate 80, pH 8.0)
25 into both deltoid muscles. The animals were immunized twice at a 4 week interval (T=0, 4 weeks).

Murine anti-RT and anti-nef ELISA - Anti-RT titers were obtained following standard secondary antibody-based ELISA. Maxisorp plates (NUNC, Rochester, NY) were coated by overnight incubation with 100 μ L of 1 μ g/mL HIV-1 RT protein
30 (Advanced Biotechnologies, Columbia, MD) in PBS. For anti-nef ELISA, 100 μ L of 1 μ g/mL HIV-1 nef (Advanced Biotechnologies, Columbia, MD) was used to coat the plates. The plates were washed with PBS/0.05% Tween 20 using Titertek MAP instrument (Huntsville, AL) and incubated for 2 h with 200 μ L/well of blocking solution (PBS/0.05% tween/1% BSA). An initial serum dilution of 100-fold was
35 performed followed by 4-fold serial dilution. 100- μ L aliquots of serially diluted samples were added per well and incubated for 2 h at room temperature. The plates

were washed and 100 μ L of 1/1000-diluted HRP-rabbit anti-mouse IgG (ZYMED, San Francisco, CA) were added with 1 h incubation. The plates were washed thoroughly and soaked with 100 μ L 1,2-phenylenediamine dihydrochloride/hydrogen peroxide (DAKO, Norway) solution for 15 min. The reaction was quenched by adding 100 μ L of 0.5M H₂SO₄ per well. OD₄₉₂ readings were recorded using Titertek Multiskan MCC/340 with S20 stacker. Endpoint titers were defined as the highest serum dilution that resulted in an absorbance value of greater than or equal to 0.1 OD₄₉₂ (2.5 times the background value).

Non-human primate and murine ELISpot assays - The enzyme-linked immuno-spot (ELISpot) assay was utilized to enumerate antigen-specific INF γ -secreting cells from mouse spleens (Miyahira, et al.1995, *J. Immunol. Methods* 181:45-54) or macaque PBMCs. Mouse spleens were pooled from 5 mice/cohort and single cell suspensions were prepared at 5×10^6 /mL in complete RPMI media (RPMI1640, 10% FBS, 2mM L-glutamine, 100U/mL Penicillin, 100 u/mL streptomycin, 10 mM Hepes, 50 uM β -ME). Rhesus PBMCs were prepared from 8-15 mL of heparinized blood following standard Ficoll gradient separation (Coligan, et al, 1998, *Current Protocols in Immunology*. John Wiley & Sons, Inc.). Multiscreen opaque plates (Millipore, France) were coated with 100 μ L/well of either 5 μ g/mL purified rat anti-mouse IFN- γ IgG1, clone R4-6A2 (Pharmingen, San Diego, CA), or 15 μ g/mL mouse anti-human IFN- γ IgG_{2a} (Cat. No. 1598-00, R&D Systems, Minneapolis, MN) in PBS at 4°C overnight for murine or monkey assays, respectively. The plates were washed with PBS/penicillin/streptomycin and blocked with 200 μ L/well of complete RPMI media for 37 °C for at least 2 h.

To each well, 50 μ L of cell samples ($4-5 \times 10^5$ cells per well) and 50 μ L of the antigen solution were added. To the control well, 50 μ L of the media containing DMSO were added; for specific responses, either selected peptides or peptide pools (4 μ g/mL per peptide final concentration) were added. For BALB/c mice immunized with the pol constructs, stimulation was conducted using a pool of CD4⁺-epitope containing 20-mer peptides (aa21-40, aa411-430, aa641-660, aa731-750, aa771-790) or a pool of CD8⁺-epitope containing peptides (aa201-220, aa311-330, aa781-800). For C57/BL6 mice immunized with the nef construct, either aa51-70 (CD8⁺ T cell epitope) or aa81-100 (CD4⁺) peptide derived from the nef sequence was added for specific stimulation. In monkeys, the responses against pol were evaluated using two pools (L and R) of 20-aa peptides that encompass the entire pol sequence and overlap by 10 amino acids. In monkeys vaccinated with the nef constructs, a single pool containing 20-mer peptides covering the entire HIV-1 nef sequence and overlapping

by 10 aa was used. Each sample/antigen mixture was performed in triplicate wells for murine samples or in duplicate wells for rhesus PBMCs. Plates were incubated at 37°C, 5% CO₂, 90% humidity for 20-24 h. The plates were washed with PBS/0.05% Tween 20 and incubated with 100 µL/well of either 1.25 µg/mL biotin-conjugated rat anti-mouse IFN-γ mAb, clone XMG1.2 (Pharmingen) or of 0.1 µg/mL biotinylated anti-human IFN-gamma goat polyclonal antibody (R&D Systems) at 4°C overnight. The plates were washed and incubated with 100 µL/well 1/2500 dilution of streptavidin-alkaline phosphatase conjugate (Pharmingen) in PBS/0.005% Tween/5% FBS for 30 min at 37 °C. Spots were developed by incubating with 100 µL/well 1-step NBT/BCIP (Pierce Chemicals) for 6-10 min. The plates were washed with water and allowed to air dry. The number of spots in each well was determined using a dissecting microscope and the data normalized to 10⁶ cell input.

Non-human Primate anti-RT ELISA - The pol-specific antibodies in the monkeys were measured in a competitive RT EIA assay, wherein sample activity is determined by the ability to block RT antigen from binding to coating antibody on the plate well. Briefly, Maxisorp plates were coated with saturating amounts of pol positive human serum (#97111234). 250 uL of each sample is incubated with 15 uL of 266 ng/mL RT recombinant protein (in RCM 563, 1% BSA, 0.1% tween, 0.1% NaN₃) and 20 uL of lysis buffer (Coulter p24 antigen assay kit) for 15 min at room temperature. Similar mixtures are prepared using serially diluted samples of a standard and a negative control which defines maximum RT binding. 200 uL/well of each sample and standard were added to the washed plate and the plate incubated 16-24 h at room temperature. Bound RT is quantified following the procedures described in Coulter p24 assay kit and reported in milliMerck units per mL arbitrarily defined by the chosen standard.

Results - Rodent Studies - BALB/c mice (n=5 mice/cohort) were immunized once or twice with varying doses of MRKAd5hCMV-IApol(E3+) and MRKAd5hCMV-IApol(E3-). At 3 weeks after the second dose, Anti-pol IgG levels were determined by an ELISA assay using RT as a surrogate antigen. Cellular response were quantified via IFNγ ELISpot assay against pools of pol-epitope containing peptides. The results of these assays are summarized in Table 10. The results indicate that the mouse vaccinees exhibited detectable anti-RT IgGs with an adenovector dose as low as 10⁷ vp. The humoral responses are highly dose-dependent and are boostable with a second immunization. One or two doses of either pol vectors elicit high frequencies of antigen-specific CD4⁺ and CD8⁺ T cells; the responses are weakly dose-dependent but are boostable with a second immunization.

Table 10. Immunogenicity of MRKAd5pol Vectors in BALB/c mice.

Group	Vaccine	Dose	No. of Doses	Anti-RT IgG Titers ^a			SFC/10 ⁶ cells ^b		
				GMT	+SE	-SE	Medium	CD4+ peptide pool	CD8+ peptide pool
1	MRKAd5hCMVFLpol (E3+)	10 ⁷ vp	2 1	310419 919	301785 372	153020 265	1(1) 1(1)	75(4) 72(9)	2313(67) 533(41)
2	MRKAd5hCMVFLpol (E3+)	10 ⁹ vp	2 1	1838400 ^c 713155	0 528520	0 303555	2(2) 1(1)	114(9) 48(7)	2083(182) 733(89)
3	MRKAd5hCMVFLpol (E3-)	10 ⁷ vp	2 1	310419 6400	386218 14013	172097 4393	0(0) 10(8)	223(7) 141(21)	2607(27) 409(28)
4	MRKAd5hCMVFLpol (E3-)	10 ⁹ vp	2 1	1838400 ^c 1241675 ^b	0 396725	0 300681	1(1) 0(0)	160(13) 39(13)	2385(11) 833(83)
5	Naïve	none	none	57	9	7	9(2)	11(4)	10(1)

^aGMT, geometric mean titer of the cohort of 5 mice; SE, standard error of the geometric mean^bNear or at the upper limit of the serial dilution; hence, could be greater than this value^cNo. of Spot-forming Cells per million splenocytes; mean values of triplicates are reported along with standard errors in parenthesis.

- 5 C57/BL6 mice were immunized once or twice with varying doses of MRKAd5hCMV-nef(G2A,LLAA) (E3+), MRKAd5mCMV-nef(G2A,LLAA) (E3+) at either 10⁷ vp and (3) MRKAd5mCMV-tpanef(LLAA) (E3+) at either 10⁷ vp and 10⁹ vp. The immune response were analyzed using similar protocols and the results are listed in Table 11. While anti-nef IgG responses could not be detected in this
- 10 model system with any of the constructs, there are strong indications of a cellular immunity generated against nef using the ELISpot assay.

Table 11. Immunogenicity of MRKAd5nef Vectors in C57/BL6 mice.

Group	Vaccine	Dose	No. of Doses	Anti-nef IgG Titers ^a			SFC/10 ⁶ cells ^b		
				GMT	+SE	-SE	Medium	aa51-70 CD8+	aa81-100 CD4+
1	MRKAd5hCMVFLnef (E3+)	10 ⁷ vp	2 1	174 132	70 42	50 32	1(1) 0(0)	23(1) 0(0)	1(1) 0(0)
2	MRKAd5hCMVFLnef (E3+)	10 ⁹ vp	2 1	174 132	70 42	50 32	0(0) 1(1)	61(7) 62(7)	4(2) 3(1)
3	MRKAd5mCMVFLnef (E3+)	10 ⁷ vp	2 1	132 115	42 48	32 33	3(1) 3(2)	15(5) 3(2)	5(2) 4(2)
4	MRKAd5mCMVFLnef (E3+)	10 ⁹ vp	2 1	132 132	42 42	32 32	4(2) 2(1)	83(13) 29(2)	5(1) 4(0)
5	MRKAd5mCMVtpanef(E3+)	10 ⁷ vp	2 1	132 100	42 0	32 0	3(2) 3(1)	14(2) 13(4)	5(1) 10(3)
6	MRKAd5mCMVtpanef(E3+)	10 ⁹ vp	2 1	230 115	170 46	98 33	3(2) 7(1)	145(29) 151(14)	4(0) 10(0)
7	Naïve	none	none	152	78	52	21(2)	18(6)	28(3)

^aGMT, geometric mean titer of the cohort of 5 mice; SE, standard error of the geometric mean^bNo. of spot-forming cells per million splenocytes; mean values of triplicates are reported along with standard errors in parenthesis.

15

Monkey Studies - Cohorts of 3 rhesus macaques were immunized with 2 doses of MRKAd5hCMV-IApol(E3+) and MRKAd5hCMV-IApol(E3-). The number of antigen-specific T cells (per million PBMCs) were enumerated using one of two

- peptide pools (L and R) that cover the entire pol sequence; the results are listed in Table 12. Moderate-to-strong T cell responses were detected in the vaccinees using either constructs even at a low dose of 10^9 vp. Longitudinal analyses of the anti-RT antibody titers in the animals suggest that the pol transgene product is expressed efficiently to elicit a humoral response (Table 13). It would appear that generally higher immune responses were observed in animals that received the E3- construct compared to the E3+ virus.

Table 12. Pol-specific T Cell Responses in MRKAd5pol Immunized Rhesus Macaques.

Vaccine (T=0,4 wks)	Monk #	Prebleed			T=4			T=7			T=16		
		Mock	Pol L	Pol R	Mock	Pol L	Pol R	Mock	Pol L	Pol R	Mock	Pol L	Pol R
MRKAd5hCMV-IAPol(E3+) 10^{11} vp	99C100	1	0	0	1	38	31	0	52	146	0	49	715
	99C215	1	2	2	10	98	249	1	109	305	22	68	250
	99D201	5	5	4	6	149	85	0	40	35	0	35	18
MRKAd5hCMV-IAPol(E3+) 10^9 vp	99D212	0	2	0	4	331	114	0	58	14	0	6	6
	99D180	0	4	2	0	19	192	4	38	156	5	38	108
	99C201	8	5	21	6	62	62	0	18	32	1	14	65
MRKAd5hCMV-IAPol(E3-) 10^{11} vp	99D239	5	2	2	20	82	172	1	66	114	9	21	40
	99C186	4	12	6	5	120	421	2	271	489	16	875	530
	99C084	1	8	9	8	84	464	0	14	236	1	24	264
MRKAd5hCMV-IAPol(E3-) 10^9 vp	CC7C	10	10	8	12	724	745	4	322	376	4	188	176
	CD1G	2	0	1	5	474	468	0	232	212	0	101	121
	CD11	6	6	12	10	98	110	5	60	80	8	25	34
Ndve	083Q	nd	nd	nd	nd	nd	nd	4	2	2	2	1	2

nd, not determined

Reported are SFC per million PBMCs; mean of duplicate wells.

Table 13. Anti-RT Ig Levels in MRKAd5pol Immunized macaques.

RT ANTIBODY ASSAY TITERS IN mMU/mL				
Vaccine/Monkey Tag	T=4	T=7	T=12	T=16
MRKAd5hCMV-IAPol(E3+), 10^{11} vp				
99C100	61	1999	5928	4768
99C215	81	1541	2356	2767
99D201	53	336	539	387
MRKAd5hCMV-IAPol(E3+), 10^9 vp				
99D212	10	40	49	68
99D180	<10	36	79	93
99C201	<10	37	71	76
MRKAd5hCMV-IAPol(E3-), 10^{11} vp				
99D239	44	460	1234	1015
99C186	21	233	480	345
99C084	235	2637	2858	1626
MRKAd5hCMV-IAPol(E3-), 10^9 vp				
CC7C	32	175	306	235
CD1G	20	140	273	419
CD11	15	112	149	237

When rhesus macaques were immunized i.m. with two doses of MRKAd5nef constructs, vigorous T cell responses ranging from 100 to as high as 1100 per million were observed in 8 of 12 vaccinees (Table 14). The efficacies of the mCMV- and hCMV- driven nef constructs are comparable on the basis of the data generated thus far.

Table 14. Nef-specific T cell Responses in MRKAd5nef Immunized Rhesus Macaques.

Vaccine (T=0,4 wks)	Monk #	Pre		T=4		T=7		T=16	
		Mock	Nef	Mock	Nef	Mock	Nef	Mock	Nef
MRKAd5hCMV-nef(G2A,LLAA) (E3+) 10 ¹¹ vp	CD2D	0	4	31	440	4	368	1	251
	CC7B	0	0	2	521	0	178	1	1522
	CC61	2	9	31	112	0	108	11	100
MRKAd5hCMV-nef(G2A,LLAA) (E3+) 10 ⁹ vp	CC2K	9	9	6	52	0	35	0	15
	CD15	5	4	30	998	2	586	0	434
	CD16	6	1	6	1146	0	369	1	212
MRKAd5mCMV-nef(G2A,LLAA) (E3+) 10 ¹¹ vp	99D191	1	5	4	614	0	298	2	419
	99D144	4	6	5	434	0	1100	2	932
	99C193	1	2	1	58	1	22	0	64
MRKAd5mCMV-nef(G2A,LLAA) (E3+) 10 ⁹ vp	99D224	1	11	14	231	1	125	0	70
	99D250	8	9	4	108	0	54	0	5
	99C120	1	6	20	299	0	92	0	79
Naïve	083Q	nd	nd	18	22	4	5	2	1

EXAMPLE 25

Comparison of Clade B vs. Clade C T Cell Responses in HIV-Infected Subjects

PBMC samples collected from two dozens of patients infected with HIV-1 in US were tested in ELISPOT assays with peptide pools of 20-mer peptides overlapping by 10 amino acids. Four different peptide pools were tested for cross-clade recognition, and they were either derived from a clade B-based isolate (gag H-b; nef-b) or a clade C-based isolate (gag H-c, nef-c). Data in Table 15 shows that T cells from these patients presumably infected with clade B HIV-1 could recognize clade C gag and nef antigens in ELISPOT assay. Correlation analysis further demonstrated that these T cell responses against clade C gag peptide pool were about 60% of the clade B counterpart (Figure 24), while the T cell responses against clade C nef were about 85% of the clade B counterpart (Figure 25). These results suggest that cellular immune responses generated in patients infected with clade B HIV-1 can recognize gag and nef antigens derived from clade C HIV-1. These data show that a HIV vaccine, such as a DNA or MRKAd5-based adenoviral vaccine expressing a clade B

gag and/or nef antigen will potentially have the ability to provide a prophylactic and/or therapeutic advantage on a global scale.

5

Table 15
Responses Shown as the Number of gIFN-Secreting T Cells per Million PBMCs

subject	bleed date	gag epitope # (from mapping)	mock	gag H-b	gagH-c	nef-b	nef-c
#100	19-Jul-99	12	10	3950	1385	1295	1300
#101	25-Jul-99	3	15	3885	1280	na	1020
#102	25-Jul-99	4	15	1740	850	1255	1785
#104	7-Jun-99	2	5	1355	1185	na	1060
#107	11-Oct-99	2	25	3305	2795	670	870
#405	11-Jul-99	2	15	4575	3180	1700	1500
#501	19-Jul-99	2	15	1100	570	3365	3460
#505	18-Jul-99	5	10	2145	1725	1235	na
#506	28-Feb-99	2	25	150	45	400	610
#701	28-Mar-99	5	30	7620	4775	3320	2780
#709	17-May-99	3	15	2785	1945	1090	1630
#710	24-May-99	4	5	1055	1080	2210	2140

10

EXAMPLE 26

Characterization and Production of MRKAd5pol and MRKAd5nef
Vectors in Roller Bottles

Expansion of nef and pol Adenovectors - Nef and pol CsCl purified MRKAd5 seeds were used to infect roller bottles to produce P4 virus to be used as a seed for further experiments. P4 MRKAd5 pol and nef vectors were used to infect roller bottles at an MOI 280 vp/cell, except for hCMV-tpa-nef [E3+] which was infected at an MOI of 125 due to low titers of seed obtained at P4.

20

Table 16 Viral particle concentrations for P5 nef and pol adenovectors

Adenovector	AEX Titer (10 ¹⁰ vp/ml culture)	AEX Titer (10 ⁴ vp/cell)	Amplification Ratio
hCMV-FL-nef [E3+]	1.1	0.9	30
mCMV-FL-nef [E3+]	2.2	2.1	75
hCMV-tpa-nef [E3+]	0.07	0.1	5
mCMV-tpa-nef [E3+]	1.3	0.9	35
hCMV-FL-pol [E3+]	2.7	2.1	75
hCMV-FL-pol [E3-]	1.9	1.3	45

- 5 *Roller Bottle Passaging* - Passaging of the *pol* and *nef* constructs continued through passage seven. Cell-associated (freeze/thaw lysis) and whole broth (triton-lysis) titers obtained in all passages were very consistent. In general, MRKAd5pol is ca. 70% as productive as MRKAd5gag while MRKAd5nef is ca. 25% as productive as MRKAd5gag. Samples of P7 virus for both constructs were analyzed by V&CB by
- 10 restriction digest analysis and did not show any rearrangements.

Table 17. Passage Six Viral Productivity for MRKAd5pol and MRKAd5nef

		Xviable (10^6 cells/ml), Viability (%)		Cell Passage Number	AEX Titer (Cell Associated) 10^{10} vp/ml culture	Titer 10^4 vp/cell	Amplification Ratio	Triton Lysis Titer 10^{10} vp/ml culture
		Infection	Harvest					
hCMV-FL-nef [E3+]	pool	1.22, 85%		62	0.8	0.7	25	1.6
	1		0.99, 62%					
	2		1.10, 72%					
hCMV-FL-pol [E3+]	pool	1.42, 89%		62	4.5	3.2	115	7.0
	1		1.22, 70%					
	2		1.42, 74%					

15 Table 18. Passage Seven Viral Productivity for MRKAd5pol and MRKAd5nef

		Xviable (10^6 cells/ml), Viability (%)		Cell Passage Number	AEX Titer (Cell Associated) 10^{10} vp/ml culture	Titer 10^4 vp/cell	Amplification Ratio	Triton Lysis Titer 10^{10} vp/ml culture
		Infection	Harvest					
hCMV-FL-nef [E3+]	Pool	1.33, 90%		66	1.0	0.8	29	2.1
	1		0.96, 70%					
	2		1.18, 73%					
hCMV-FL-pol [E3+]	Pool	0.90*, 90%		56	4.2	4.7	168	6.5
	1		1.18, 88%					
	2		1.04, 80%					

- MRKAd5nef and MRKAd5pol Viral Production Kinetics* - A timecourse experiment was carried out in roller bottles to determine if the viral production kinetics of the MRKAd5pol and MRKAd5nef vectors were similar to those of MRKAd5gag. PER.C6[®] cells in roller bottle cultures were infected at an MOI of 280 vp/cells with P5 MRKAd5pol, P5 MRKAd5nef and P7 MRKAd5gag; for each adenovector, two infected bottles were sampled at 24, 36, 48, and 60 hours post infection. In addition, two bottles were left unsampled until 48 hpi when they were harvested under the Phase I process conditions. The anion-exchange HPLC viral
- 20 particle concentrations of the freeze-thaw recovered cell associated virus at the 24, 36,
- 25

48, and 60 hpi timepoints are shown in Figure 29A-B. The QPA titers show a similar trend (data not shown).

Comparison of hCMV- and mCMV-FL-nef - As the titers obtained with the MRKAd5nef construct (hCMV-FL-nef) were lower than those obtained with MRKAd5gag or MRKAd5pol, a viral productivity comparison experiment was performed with mCMV-FL-nef. For each of the two adenovectors (hCMV- and mCMV-FL-nef), two roller bottles were infected at an MOI of 280 vp/cell with passage five clarified lysate. The macroscopic and microscopic observations of the four roller bottles were identical at the time of harvest. Analysis of the clarified lysate produced indicated a higher viral particle concentration in the bottles infected with mCMV-FL-nef, as shown in Table 19. It is stipulated that the higher productivity with mCMV promoter driven nef vector is due to lower nef expression levels in PER.C6[®] cells- experiments are underway at V&CB to measure nef expression levels.

Table 19. Passage Six Viral Productivity Comparison of hCMV- and mCMV-FL-nef

		Xv (10 ⁶ cells/ml), Viability (%)		Cell Passage	AEX Titer	Titer	Amplification	Triton Lysis Titer
		Infection	Harvest	Number	10 ¹⁰ vp/ml culture	10 ⁴ vp/cell	Ratio	10 ¹⁰ vp/ml culture
hCMV-FL-nef (MRKAd5nef)	Pool	1.11, 91%		60	1.5	1.4	50	2.8
	1		1.23, 75%					
	2		1.34, 74%					
mCMV-FL-nef	Pool	1.11, 91%		60	2.3	2.1	75	4.6
	1		1.49, 84%					
	2		1.18, 77%					

20

EXAMPLE 27

Characterization and Large Scale Production of MRKAd5nef Virus in Bioreactors

Materials and Methods - The experiment of the present example was run twice under the following conditions: 36.5°C, DO 30%, pH 7.30, 150rpm agitation rate, no sparging, Life Technologies (Gibco, Invitrogen) 293 SFM II (with 6mM L-glutamine), 0.5M NaOH as base for pH control. During the first run (B20010115), two 10L stirred vessel bioreactors were inoculated with PER.C6[®] cells at a concentration of 0.2x10⁶ cells/ml. Cells were grown until they reached a cell concentration of approximately 1x10⁶ cells/ml. The cells were infected with uncloned MRKAd5nef (G2A,LLAA) at a MOI of 280 virus particles (vp)/cell. For the second batch (B20010202), the same procedure as the first run was used, except the cells

were infected with cloned MRAd5nef. During both runs, the bioreactors were harvested 48 hours post-infection. Samples were taken and virus concentrations were determined from whole broth (with triton lysis), supernatant, and cell pellets (3 X freeze/thaw) with the AEX and QPA assays. Metabolites were measured with BioProfile 250 throughout the process.

Table 20: Experimental Conditions

Temperature	36.5 °C
DO	30%
PH	7.30
Agitation	150 rpm
Sparging	None

Table 21: Virus source used for experiments.

Run	Batch ID	Cloned/Uncloned MRKAd5nef	MOI (vp/cells)
#1	B20010115-1	Uncloned	280
	B20010115-2	Uncloned	280
#2	B20010202-1	Cloned	280
	B20010202-2	Cloned	280

Results - Table 22 and 23 show an the ability to scale up production of MRKAd5nef by growth in a bioreactor.

Table 22: Virus Concentration as measured by the AEX assay

Run	Batch ID	Cloned/Uncloned MRKAd5nef	Virus Concentration @ 48hpi (1x10 ¹⁵ vp/L)			
			Supernatant	Clarified Lysate	Total	Triton Lysate
#1	B20010115-1	Uncloned	0.72	3.26	3.98	5.76
	B20010115-2	Uncloned	0.38	1.67	2.05	2.46
#2	B20010202-1	Cloned	0.80	6.00	6.80	8.88
	B20010202-2	Cloned	0.50	6.00	6.50	8.47

Table 23: Virus Titers as measured by the QPA assay

Run	Batch ID	Cloned/Uncloned MRKAd5nef	Virus Concentration @ 48hpi (1x10 ¹¹ IU/L)				
			Whole Broth	Supernatant	Clarified Lysate	Total	Triton Lysate
#1	B20010115-1	Uncloned	0.13	1.12	1.76	2.88	11.28
	B20010115-2	Uncloned	0.14	0.73	1.54	2.27	5.86
#2	B20010202-1	Cloned	0.14	0.97	1.62	2.69	11.89
	B20010202-2	Cloned	0.14	1.17	1.70	2.97	12.47

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art

from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

EXAMPLE 28

MRKAd5HIV-1gag Boosting of DNA-Primed Animals

Groups of 3-5 rhesus macaques were immunized with (a) 5 mgs of V1Jns-Flgag (pV1JnsCMV(no intron)-FL-gag-bGHpA), (b) 5 mgs of V1Jns-Flgag formulated with 45 mgs of a non-ionic block copolymer CRL1005, or (c) 5 mgs of V1Jns-Flgag formulated with 7.5 mgs of CRL1005 and 0.6 mM benzalkonium chloride at weeks 0, 4, and 8. All animals received a single dose of 10^7 viral particles (vp) of the MRKAd5HIV-1gag at week 26. Note: 10^7 is too low to prime or boost effectively when used as a single modality (dose is selected to mimic preexposure to adenovirus); see Figure 32.

Blood samples were collected from all animals at several time points and peripheral blood mononuclear cells (PBMCs) were prepared using standard Ficoll method. The PBMCs were counted and analyzed for gamma-interferon secretion using the ELISpot assay (Table 24). For each monkey, the PBMCs were incubated overnight either in the absence (medium) or presence of a pool (called "gag H") of 50 20-aa long peptides that encompass the entire HIV-1 gag sequence.

The results indicate that MRKAd5HIV-1gag was very effective in boosting the T cell immune responses in these monkeys. At week 28 or 2 weeks after the viral boost, the number of gag-specific T cells per million PBMCs increased 2-48 fold compared to the levels observed at week 24 or 2 weeks prior to the boost.

The PBMCs were also analyzed by intracellular gamma-interferon staining prior to (at week 10) and after the MRKAd5gag boost (at week 30). The results for select animals are shown on Figure 31. The results indicate that (a) immunization with DNA/adjuvant formulation elicited T cell responses which can either be balanced, $CD4^+$ -biased or $CD8^+$ -biased, and (b) boosting with the MRKAd5gag construct produced in all cases a strongly $CD8^+$ -biased response. These results suggest that boosting with MRKAd5HIV-1gag construct is able to improve the levels of antigen-specific $CD8^+$ T cells.

Table 24. Boosting of DNA/Adjuvant-Primed Rhesus Monkeys with MRKAd5gag
Number of 8FChilliton PBMCs

Grp#	Priming T=0, 4, 8 wks	Boost T=28 wks	Month#	T=0		T=4		T=6		T=10		T=17		T=24		T=28		T=30	
				Medium	gag H	Medium	gag H	Medium	gag H	Medium	gag H	Medium	gag H	Medium	gag H	Medium	gag H	Medium	gag H
1	DNA5 mgs PBS (D101)	MRKAd5gag(E3+) 10 ⁷ vp	CB5H CB5K AW3J3	NA 0 5	NA 0 11	3 0 0	35 15 0	15 0 3	71 48 51	4 0 3	224 58 48	8 0 2	115 75 89	8 0 8	65 35 65	18 3 10	956 1705 989	0 1 0	316 755 395
2	DNA5mgs + CRL1005/45mgs	MRKAd5gag(E3+) 10 ⁷ vp	CG1C CG1K AW3P CB5F AK8B	0 4 9 NA 9	4 0 8 NA 12	1 1 1 0 4	60 101 10 31 38	0 0 4 0 1	111 254 71 288 119	5 0 4 0 0	270 781 184 530 439	4 5 8 19 0	280 482 104 374 425	8 6 8 9 0	232 321 65 251 316	3 0 11 8 4	959 1916 838 1549 1229	19 1 6 20 5	1345 1089 241 1734 1354
3	DNA5 mgs+ CRL1005/7.5 mgs + 0.8 mM BAK	MRKAd5gag(E3+) 10 ⁷ vp	AW20 CA4R CB5B CB5W CB7D	10 1 8 4 1	4 0 6 3 0	1 3 0 0 0	59 121 8 26 138	5 1 3 1 0	284 135 119 91 316	19 1 0 0 1	425 270 274 139 599	6 5 6 0 5	105 130 282 184 625	9 1 1 1 1	205 105 209 82 759	19 14 0 5 0	565 1384 638 543 2278	9 10 1 1 4	404 978 828 349 1831
4	none	None	8BQ201	3	0	0	0	1	0	0	0	0	1	1	2	3	0	0	0

NA, not available

EXAMPLE 29

Construction of gagpol fusion for MRKAd5gagpol fusion constructs

The open reading frames for the codon-optimized HIV-1 gag gene was fused
5 directly to the open reading frame of the IA pol gene (consisting of RT, RNaseH and
integrase domains) by stepwise PCR. Because the gene (SEQ ID NO: 38) does not
include the protease gene and the frameshift sequence, it encodes a single polypeptide
of the combined size of p55, RT, RNase H and integrase (1350 amino acids; SEQ ID
NO: 39).

10 The fragment that extends from the BstEII site within the gag gene to the last
non-stop codon was ligated via PCR to a fragment that extends from the start codon
of the IAPol to a unique BamHI site. This fragment was digested with BstEII and
BamHI. Construction of gag-IAPol fusion was achieved via three-fragment ligation
involving the PstI-BstEII gag digestion fragment, the BstEII/BamHI digested PCR
15 product and long PstI/BamHI V1R-FLpol backbone fragment.

The MRKAd5-gagpol adenovirus vector was constructed using the BglII
fragment of the V1R-gagpol containing the entire ORF of gag-IAPol fusion gene.

EXAMPLE 30

Immunogenicity Studies in Non-Human Primates

20 Cohorts of three (3) macaques were immunized with 10e8 or 10e10 viral
particles (vp) of one of the following MRKAd5 HIV-1 vaccines: (1) MRKAd5gag;
(2) MRKAd5pol; (3) MRKAd5nef; (4) a mixture containing equal amounts of
25 MRKAd5gag, MRKAd5pol, and MRKAd5nef, or (5) a mixture of equal amounts of
MRKAd5gagpol and MRKAd5nef. The vaccines were administered at weeks 0 and
4.

The T cell responses against each of the HIV-1 antigens were assayed by IFN-
gamma ELISpot assay using pools of 20-aa peptides that encompass the entire protein
30 sequence of each antigen. The results (Table 25) are expressed as the number of spot-
forming cells (sfc) per million peripheral blood mononuclear cells (PBMC) that
respond to each of the peptide pools.

Results indicate the following observations: (1) each of the single gene
constructs (MRKAd5gag, MRKAd5pol, or MRKAd5nef) is able to elicit high levels
35 of antigen-specific T cells in monkeys; (2) the single-gene MRKAd5 constructs can
be mixed as a multi-cocktail formulation capable of eliciting very broad T cell
responses against gag, pol, and nef; (3) the MRKAd5 vector expressing the fusion

protein of gag plus IA pol is capable of inducing strong T cell responses to both gag and pol.

Table 25. Evaluation of Mixtures of MRKAd5 vectors expressing humanized HIV-1 gag, pol, gagpol, nef in rhesus macaques

Grp #	Vaccine T=0, 4 wks	Monk #	T=6 wks				
			Mock	Gag H	Pol - 1	Pol - 2	Nef
1	MRKAd5 gag 10 ¹⁰ vp	CB9V	0	15	-	-	-
		CD19	0	374	-	-	-
		109H	1	843	-	-	-
2	MRKAd5 gag 10 ⁸ vp	99D130	1	948	-	-	-
		W277	16	324	-	-	-
		143H	4	595	-	-	-
3	MRKAd5 pol 10 ¹⁰ vp	CC1X	4	-	46	256	-
		AW3W	3	-	463	550	-
		AV43	6	-	95	1333	-
4	MRKAd5 pol 10 ⁸ vp	AW38	1	-	19	30	-
		CC8K	0	-	50	995	-
		CC21	1	-	33	436	-
5	MRKAd5 nef 10 ¹⁰ vp	076Q	9	-	-	-	1204
		091Q	4	-	-	-	85
		083Q	0	-	-	-	176
6	MRKAd5 nef 10 ⁸ vp	00C029	1	-	-	-	114
		98D022	6	-	-	-	170
		98D160	3	-	-	-	198
7	MRKAd5gag+MRKAd5pol+MRKAd5nef 10 ¹⁰ vp each	99D251	3	206	15	193	120
		05H	3	135	21	9	638
		00C016	3	26	4	51	23
8	MRKAd5gag+MRKAd5pol+MRKAd5nef 10 ⁸ vp each	99D215	1	171	18	193	240
		81H	5	73	6	14	243
		12H	8	1140	115	811	719
9	MRKAd5gagpol +MRKAd5 nef 10 ¹⁰ vp each	99D211	0	83	56	838	725
		22H	4	385	119	1194	1915
		61H	4	343	11	765	853
10	MRKAd5gagpol +MRKAd5 nef 10 ⁸ vp each	34H	3	78	19	5	75
		48H	1	65	105	46	43
		70H	5	158	15	220	191

Indicated are numbers of spot-forming cells per million PBMCs against the peptide pools. Mock, no peptides; gag H, fifty 20-aa peptides encompassing p55 sequence; pol-1, 20-aa peptides representing N-terminal half of IA pol; pol-2, 20-aa peptides representing the carboxy-terminal half of IA pol; nef, 20-aa peptides encompassing the entire wild-type nef sequence. Responses to the antigens prior to the first immunization did not exceed 40 sfc/10⁶ PBMC.

WHAT IS CLAIMED IS

:

1. A recombinant adenoviral vaccine vector at least partially deleted in
5 E1 and devoid of E1 activity, comprising:
 - a) an adenovirus *cis*-acting packaging region corresponding to from
about base pair 1 to between from about base pair 400 to about
base pair 458 of a wildtype adenovirus genome; and
 - b) a gene encoding an HIV protein or immunologically relevant
10 modification thereof.
2. A vector in accordance with claim 1 comprising a packaging region
corresponding to from about base pair 1 to about base pair 450 of a wildtype
adenovirus genome.
3. A vector in accordance with claim 1 further comprising nucleotides
15 corresponding to between from about base pair 3511 to about 3524 to about base pair
5798 of a wildtype adenovirus genome.
4. A vector in accordance with claim 3 comprising base pairs
corresponding to 1-450 and 3511-5798 of a wildtype adenovirus genome.
5. A vector in accordance with claim 4 which is deleted of base pairs
20 451-3510.
6. A vector in accordance with claim 1 which is at least partially
deleted in E3.
7. A vector in accordance with claim 6 wherein the E3 deleted region
is from base pairs 28,133-30,818.

8. A vector in accordance with claim 1 wherein the gene encoding the HIV protein or modification thereof comprises codons optimized for expression in a human.

9. A vector in accordance with claim 1 wherein the vector comprises a
5 gene expression cassette comprising:

a) a nucleic acid encoding a protein;

b) a heterologous promoter operatively linked to the nucleic acid encoding the protein; and

(c) a transcription termination sequence.

10 10. A vector in accordance with claim 9 wherein the gene expression cassette is inserted into the E1 region.

11. An adenoviral vector in accordance with claim 9 wherein the gene expression cassette is in an E1 parallel orientation

12. An adenoviral vector in accordance with claim 9 wherein the gene
15 expression cassette is in an E1 antiparallel orientation.

13. An adenoviral vector in accordance with claim 9 wherein the promoter is a cytomegalovirus promoter devoid of intronic sequences.

14. An adenoviral vector in accordance with claim 13 wherein the promoter is an immediate early human cytomegalovirus promoter.

20 15. An adenoviral vector in accordance with claim 9 wherein the promoter is a murine cytomegalovirus promoter.

16. An adenoviral vector in accordance with claim 9 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

17. An adenoviral vector in accordance with claim 9 wherein the transcription termination sequence is a synthetic polyadenylation signal (SPA).

18. A cell comprising the adenoviral vector of claim 1.

19. Recombinant, replication-defective adenovirus particles harvested
5 and purified subsequent to transfection of the adenoviral vector of claim 1 into a cell line which expresses adenovirus E1 protein at complementing levels.

20. An HIV vaccine composition comprising purified adenovirus particles of claim 19.

21. An HIV vaccine composition of claim 20 which comprises a
10 physiologically acceptable carrier.

22. A method of producing recombinant, replication defective adenovirus particles containing the adenoviral genome of the adenoviral vector of claim 1 which comprises introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and harvesting the resultant recombinant,
15 replication-defective adenovirus.

23. A method according to claim 22 wherein the cell is a PER.C6[®] cell.

24. A method of generating a cellular-mediated immune response against HIV in an individual comprising administering to the individual a vaccine of
20 claim 21.

25. A method according to claim 24 which further comprises administration to the individual a DNA plasmid vaccine, optionally administered with a biologically effective adjuvant, protein or other agent capable of increasing the immune response.

26. A method according to claim 25 wherein the DNA plasmid vaccine is administered to the individual prior to administration of an adenovirus vaccine.

27. A method according to claim 24 wherein the adenovirus vaccine is preceded by an adenovirus vaccine of a different serotype.

28. A method according to claim 24 which comprises administering and readministering the adenovirus vaccine vector to the individual.

29. An adenoviral vector in accordance with claim 1 wherein the HIV protein is HIV gag or an immunologically relevant modification thereof.

30. An adenoviral vector in accordance with claim 9 wherein the gene expression cassette comprises an open reading frame encoding an HIV gag protein or immunologically relevant modification thereof.

31. A recombinant adenoviral vaccine vector at least partially deleted in E1 and devoid of E1 activity, comprising:

- a) an adenovirus *cis*-acting packaging region corresponding to from about base pair 1 to about base pair 450 and from about 3511 to about 5798 of a wildtype adenovirus genome, and deleted for base pairs corresponding to from about base pair 451 to from about base pair 3510 of a wildtype adenovirus genome; and
- b) a gene expression cassette comprising
- i) SEQ ID NO: 29;
 - ii) a heterologous promoter operatively linked to i); and
 - iii) a transcription termination sequence.

32. An adenoviral vector in accordance with claim 31 wherein the gene expression cassette is in an E1 parallel orientation.

33. An adenoviral vector in accordance with claim 31 wherein the gene expression cassette is in an E1 antiparallel orientation.

5 34. An adenoviral vector in accordance with claim 31 wherein the promoter is a cytomegalovirus promoter devoid of intronic sequences.

35. An adenoviral vector in accordance with claim 31 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

10 36. An adenoviral vector in accordance with claim 31 which is at least partially deleted in E3.

37. A cell comprising the adenoviral vector of claim 30.

38. Recombinant, replication-defective adenovirus particles harvested and purified subsequent to transfection of the adenoviral vector of claim 30 into a cell
15 line which expresses adenovirus E1 protein at complementing levels.

39. An HIV vaccine composition comprising purified adenovirus particles of claim 38.

40. An HIV vaccine composition of claim 39 which comprises a physiologically acceptable carrier.

20 41. A method of producing recombinant, replication defective adenovirus particles containing the adenoviral genome of the adenoviral vector of claim 30 which comprises introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and harvesting the resultant recombinant, replication-defective adenovirus.

42. A method according to claim 41 wherein the cell is a PER.C6[®] cell.

43. A method of generating a cellular-mediated immune response against HIV in an individual comprising administering to the individual a vaccine of
5 claim 21.

44. A method according to claim 43 which further comprises administration to the individual a DNA plasmid vaccine, optionally administered with a biologically effective adjuvant, protein or other agent capable of increasing the immune response.

10 45. A method according to claim 44 wherein the DNA plasmid vaccine is administered to the individual prior to administration of an adenovirus vaccine.

46. A method according to claim 43 wherein the adenovirus vaccine is preceded by an adenovirus vaccine of a different serotype.

15 47. A method according to claim 43 which comprises administering and readministering the adenovirus vaccine vector to the individual.

48. An adenoviral vector in accordance with claim 1 wherein the HIV protein is HIV pol or an immunologically relevant modification thereof.

49. An adenoviral vector in accordance with claim 9 wherein the gene
20 expression cassette comprises an open reading frame encoding an HIV pol protein or immunologically relevant modification thereof.

50. A recombinant adenoviral vaccine vector at least partially deleted in E1 and devoid of E1 activity, comprising:

a) an adenovirus *cis*-acting packaging region corresponding to from about base pair 1 to about base pair 450 and from about 3511 to about 5798 of a wildtype adenovirus genome, and deleted for base pairs corresponding to from about base pair 451 to from about base pair 3510 of a wildtype adenovirus genome; and

b) a gene expression cassette comprising

- i) a nucleotide sequence selected the group consisting of SEQ ID NO: 1, SEQ ID NO: 5 and SEQ ID NO: 7;
- ii) a heterologous promoter operatively linked to i); and
- iii) a transcription termination sequence.

51. An adenoviral vector in accordance with claim 50 wherein the gene expression cassette is in an E1 parallel orientation.

52. An adenoviral vector in accordance with claim 50 wherein the gene expression cassette is in an E1 antiparallel orientation.

53. An adenoviral vector in accordance with claim 50 wherein the promoter is a cytomegalovirus promoter devoid of intronic sequences.

54. An adenoviral vector in accordance with claim 50 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

55. An adenoviral vector in accordance with claim 50 which is at least partially deleted in E3.

56. A cell comprising the adenoviral vector of claim 49.

57. Recombinant, replication-defective adenovirus particles harvested and purified subsequent to transfection of the adenoviral vector of claim 49 into a cell line which expresses adenovirus E1 protein at complementing levels.

58. An HIV vaccine composition comprising purified adenovirus
5 particles of claim 57.

59. An HIV vaccine composition of claim 58 which comprises a physiologically acceptable carrier.

60. A method of producing recombinant, replication defective adenovirus particles containing the adenoviral genome of the adenoviral vector of
10 claim 49 which comprises introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and harvesting the resultant recombinant, replication-defective adenovirus.

61. A method according to claim 60 wherein the cell is a PER.C6[®] cell.

15 62. A method of generating a cellular-mediated immune response against HIV in an individual comprising administering to the individual a vaccine of claim 59.

63. A method according to claim 62 which further comprises administration to the individual a DNA plasmid vaccine, optionally administered with
20 a biologically effective adjuvant, protein or other agent capable of increasing the immune response.

64. A method according to claim 63 wherein the DNA plasmid vaccine is administered to the individual prior to administration of an adenovirus vaccine.

65. A method according to claim 62 wherein the adenovirus vaccine is preceded by an adenovirus vaccine of a different serotype.

66. A method according to claim 62 which comprises administering and readministering the adenovirus vaccine vector to the individual.

5 67. An adenoviral vector in accordance with claim 1 wherein the HIV protein is HIV nef or an immunologically relevant modification thereof.

68. An adenoviral vector in accordance with claim 9 wherein the gene expression cassette comprises an open reading frame encoding an HIV nef protein or immunologically relevant modification thereof.

10 69. A recombinant adenoviral vaccine vector at least partially deleted in E1 and devoid of E1 activity, comprising:

a) an adenovirus *cis*-acting packaging region corresponding to from about base pair 1 to about base pair 450 and from about 3511 to about 5798 of a wildtype adenovirus genome, and deleted for base pairs corresponding to from about base pair 451 to from about base pair 3510 of a wildtype adenovirus genome; and

b) a gene expression cassette comprising

i) a nucleotide sequence selected the group consisting of SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13 and SEQ ID NO: 15;

ii) a heterologous promoter operatively linked to i); and

iii) a transcription termination sequence.

70. An adenoviral vector in accordance with claim 69 wherein the gene expression cassette is in an E1 parallel orientation.

71. An adenoviral vector in accordance with claim 69 wherein the gene expression cassette is in an E1 antiparallel orientation.

72. An adenoviral vector in accordance with claim 69 wherein the promoter is a cytomegalovirus promoter devoid of intronic sequences.

5 73. An adenoviral vector in accordance with claim 69 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

74. An adenoviral vector in accordance with claim 69 which is at least partially deleted in E3.

10 75. A cell comprising the adenoviral vector of claim 68.

76. Recombinant, replication-defective adenovirus particles harvested and purified subsequent to transfection of the adenoviral vector of claim 68 into a cell line which expresses adenovirus E1 protein at complementing levels.

15 77. An HIV vaccine composition comprising purified adenovirus particles of claim 76.

78. An HIV vaccine composition of claim 77 which comprises a physiologically acceptable carrier.

79. A method of producing recombinant, replication defective adenovirus particles containing the adenoviral genome of the adenoviral vector of claim 68 which comprises introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and harvesting the resultant recombinant, replication-defective adenovirus.

80. A method according to claim 79 wherein the cell is a PER.C6[®] cell.

81. A method of generating a cellular-mediated immune response against HIV in an individual comprising administering to the individual a vaccine of claim 78.

82. A method according to claim 81 which further comprises
5 administration to the individual a DNA plasmid vaccine, optionally administered with a biologically effective adjuvant, protein or other agent capable of increasing the immune response.

83. A method according to claim 82 wherein the DNA plasmid vaccine is administered to the individual prior to administration of an adenovirus
10 vaccine.

84. A method according to claim 81 wherein the adenovirus vaccine is preceded by an adenovirus vaccine of a different serotype.

85. A method according to claim 81 which comprises administering and readministering the adenovirus vaccine vector to the individual.

15 86. A multivalent adenovirus vaccine composition comprising recombinant, replication-defective adenovirus particles, wherein the adenovirus particles are harvested and purified from a cell line expressing adenovirus E1 protein, and wherein the particles are harvested subsequent to transfection of the cells with an adenoviral vector or vectors in accordance with claim 9; said vector(s) comprising a
20 gene expression cassette or cassettes comprising nucleotide sequences encoding HIV proteins selected from the group consisting of:

- a) gag, pol, and nef, expressed independently from three individual vectors;

- b) gag, pol, and nef, expressed independently from one vector with the encoding nucleic acid sequences operatively linked to distinct promoters and transcription termination sequences;
- c) gag, pol, and nef, expressed via two vectors, one expressing a pol-nef fusion, and another expressing gag;
- 5 d) gag, pol, and nef, expressed via two vectors, one expressing a gag-pol fusion and another expressing nef;
- e) gag, pol and nef, expressed via two vectors, one expressing a nef-gag fusion and another expressing pol;
- 10 f) gag, pol, and nef, expressed via one vector expressing a gag-pol-nef fusion;
- g) gag and pol, expressed independently from two individual vectors;
- h) gag and pol, expressed independently from one vector with the encoding nucleic acid sequences operatively linked to distinct promoters and transcription termination sequences;
- 15 i) pol and nef, expressed independently from two individual vectors;
- j) pol and nef, expressed independently from one vector with the encoding nucleic acid sequences operatively linked to distinct promoters and transcription termination sequences;
- 20 k) nef and gag, expressed independently from two individual vectors;
- l) nef and gag, expressed independently from one vector with the encoding nucleic acid sequences operatively linked to distinct promoters and transcription termination sequences;
- m) gag and pol, expressed via one vector expressing a gag-pol fusion;

n) pol and nef, expressed via one vector expressing a pol-nef fusion;

and

o) nef and gag, expressed via one vector expressing a nef-gag fusion.

87. A multivalent adenovirus vaccine composition in accordance with
5 claim 86 wherein the gag-pol fusion consists of SEQ ID NO: 39.

88. A multivalent adenovirus vaccine composition in accordance with
claim 86 wherein the fused sequences have the encoding nucleic acid sequences
operatively linked to distinct promoters and transcription termination sequences.

89. A multivalent adenovirus vaccine composition in accordance with
10 claim 86 wherein the fused sequences have the encoding nucleic acid sequences
operatively linked to a single promoter; and the encoding nucleic acid sequences
operatively linked by an internal ribosome entry sequence ("IRES").

Original Adenovector Construct:

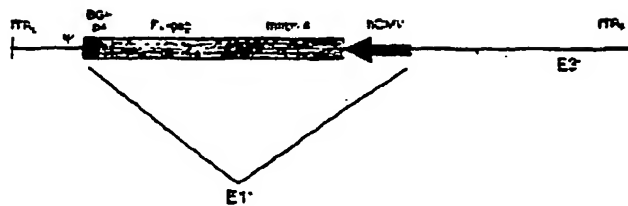


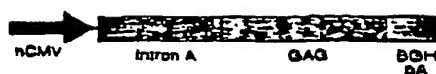
Figure 1: Original HIV-1 gag adenovector.

Sequence of the open reading frame for FL-gag (human codon optimized)

atgggtgctagggcttcgtgctgctggtggtagctggacaagtgggagaagatcaggctgaggcctgggg
caagaagaagtacaagctaaagcacatigtggtggccctcaggaggctggagagggttgctggaacccctggc
ctgctggagacctctgaggggtgcaggcagatcctggggccagctccagccctccctgcaaacaggctctgagg
agctgagggtccctgtacaacacagtggctaccctgtactgtgaccagaagatgatggaaggacaccaag
gaggccctggagaagatgaggaggagcagaacaagtccaagaagaaggccagcaggctgctgctggc
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acgtggtggccctgtgccccggccagatgaggaggccagggtctgacatgtctggcaccacctccacct
ccaggagcagatggctggatgaccaacaaccccccatcctgtgggggaaatctacaagagggtggatcat
cctgggctgaacaagatgtgaggatgtactccccaccctccatcctggacatcaggcagggtccccaaggag
ccctcagggaactatgtggacagggttctacaagacctgagggtgagcaggccctccaggagggtgaagaact
ggatgacagagacctgctggtagcagaatgccaaacctgactgcaagacctcctgaaggccctgggcccctg
ctgccacctggaggagatgatgacagccigccagggtggggggccctgggtcacaaggccagggtgtctg
gctgaggccatgtcccagggtgaccaactccgccaccaatcatgatgagagggtgcaacttcagggaaccagag
gaagacagtgaagtgtctcaactgtggcaagggtgggccacattgccagaactgtagggtcccccagggaaga
agggtgtctgggaagtgtggcaaggagggtccaccagatgaaggactgcaatgagaggcaggccaacttctg
ggcaaaa!ctggcccctccacaagggtgaggccctggcaacttctccagtcaggccctgagcccacagcccct
cccgaggagtcttcagggttggggaggagaagaccaacccagccagaagcaggagcccatgacaagg
agctgtacccccctggccctccctgagggtccctgttggcaacgacccctcctccaglaaaataaagcccgggca
gat (SEQ ID NO: 29)

Figure 2

Old Transgene:



New Transgenes:

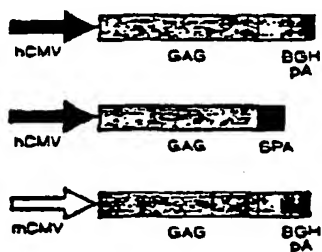


Figure 3: Diagrammatic representation of the original HIV-1 gag transgene and the series of new transgene constructions.

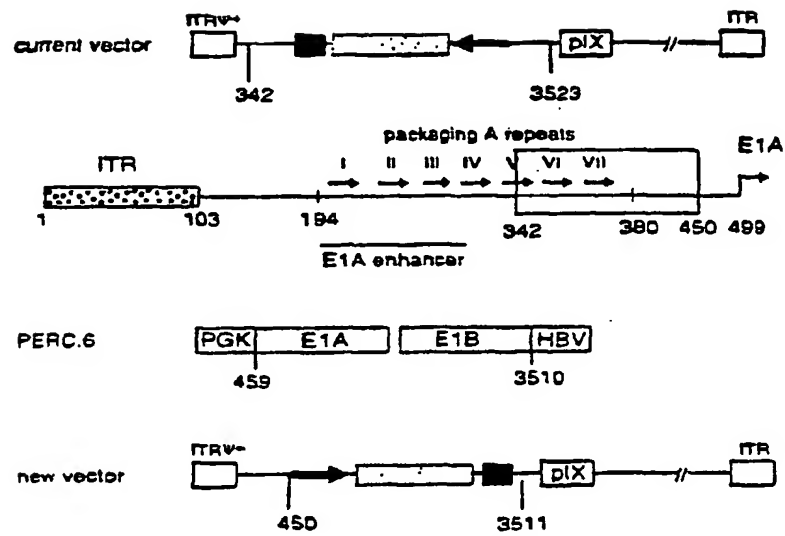


Figure 4: Modifications made to the current adenovector backbone in the generation of the new vector.

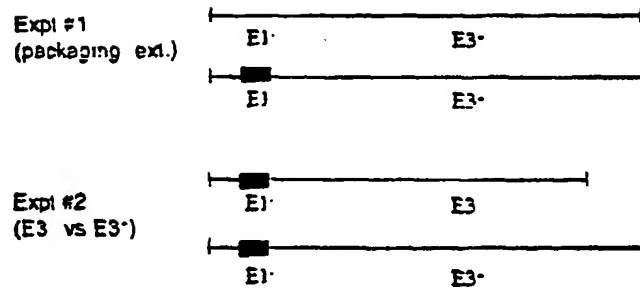


Figure 5: Virus mixing experiments to determine the effects of the addition made to the packaging signal region (Expt #1) and analysis of the effects of the E3 gene on viral growth (Expt. #2). The red bars denote the region of modifications made to the E1 deletion.

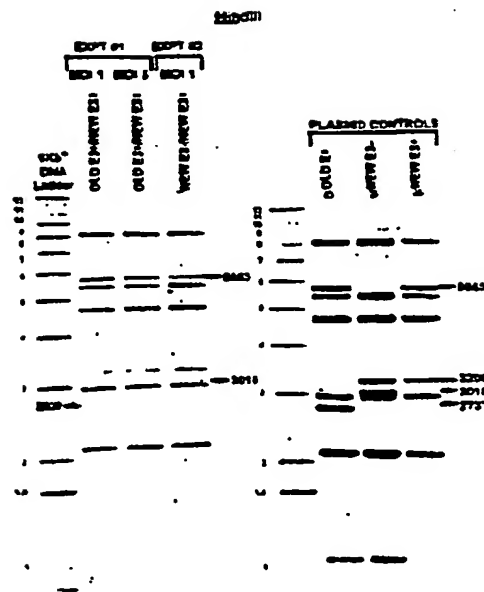


Figure 6: Autoradiograph of viral DNA analysis following viral mixing experiments (expts. #1 and #2) as detailed in the text.

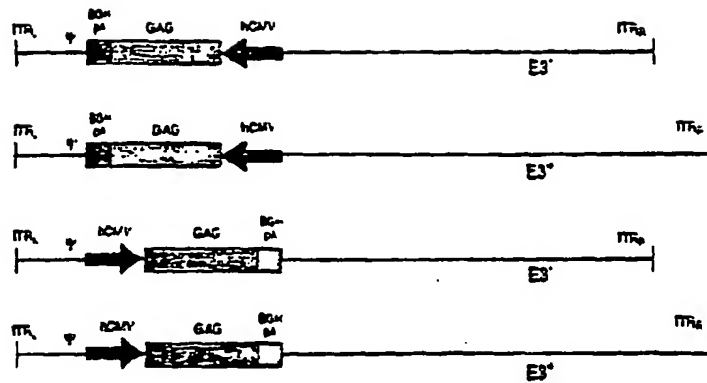


Figure 7A: hCMV-FLgag-bGHpA adenovectors constructed within the "MRK" backbone. E1 parallel and E1 antiparallel transgene orientation within the E3⁻ and E3⁺ backbones were constructed.

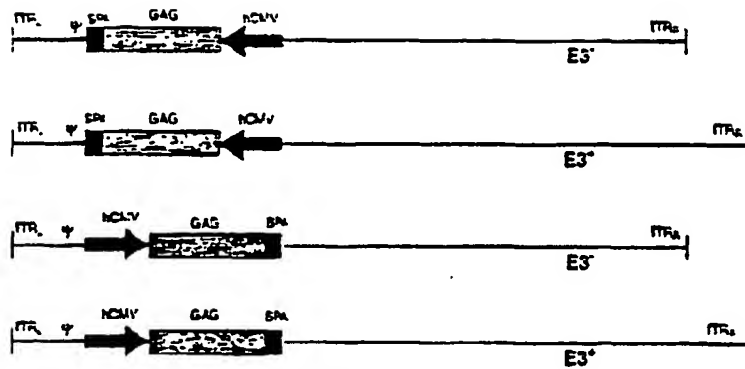


Figure 7B: hCMV-FLgag-SPA adenovectors constructed within the "MRK" backbone. E1 parallel and E1 antiparallel transgene orientation within the E3⁻ and E3⁺ backbones were constructed.

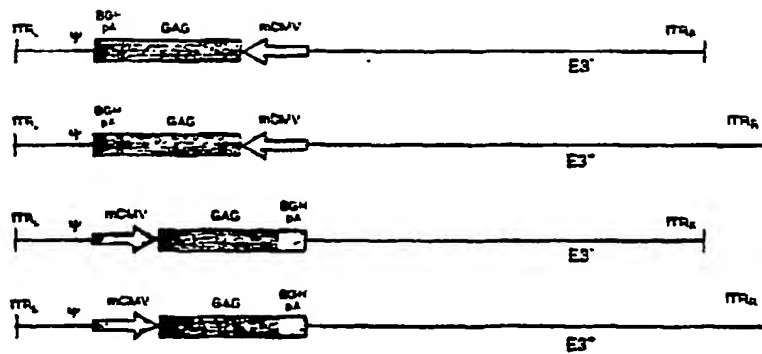


Figure 7C: mCMV-FLgag-bGHpA adenovectors constructed within the "MRK" backbone. E1 parallel and E1 antiparallel transgene orientation within the E3⁻ and E3⁺ backbones were constructed.

Plasmid mixing expt: (orientation)

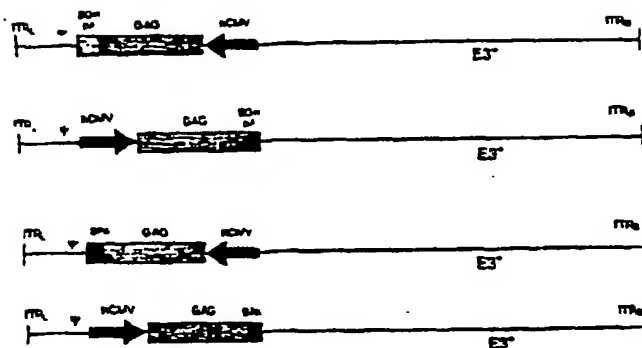


Figure 8A: Effect of transgene orientation

Plasmid Mixing expt: (poly A signal)

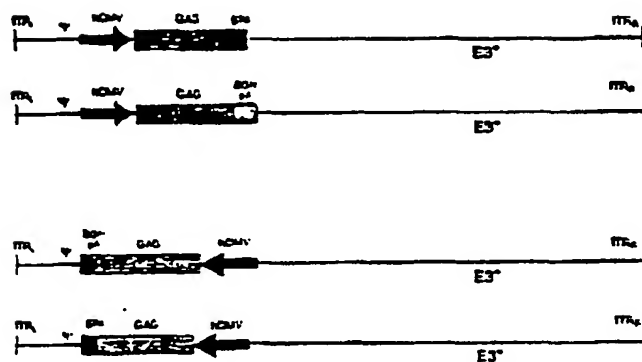


Figure 8B: Effect of polyadenylation signal



Figure 9: Viral DNA from the four Adgag candidates at P5, following *BstE11* digestion.

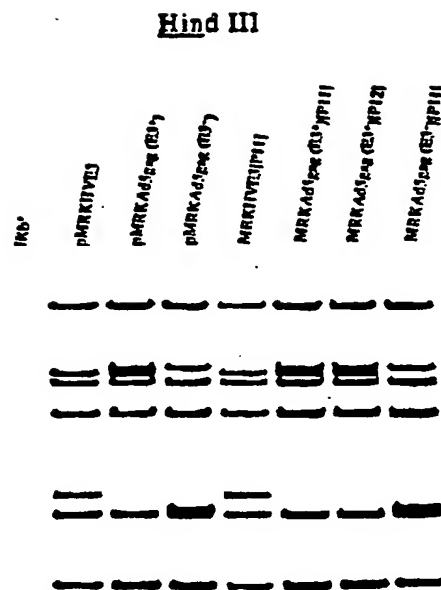


Figure 10: Viral DNA analysis of passage 11 and/or 12 of MRKHVE3, MRKAd5gag and MRKAd5gag(E3-).

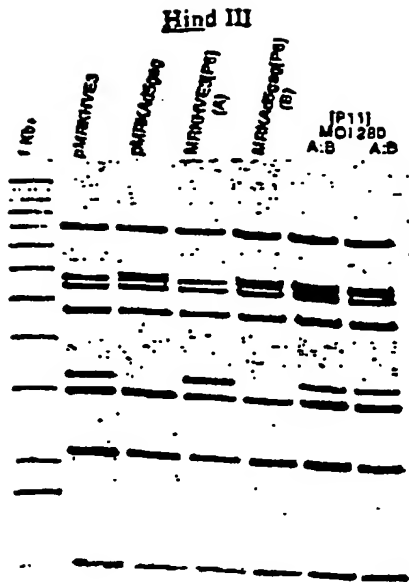


Figure 11: Viral DNA analysis (*Hind*III digestion) of passage 6 MRKHVE3 and MRKAd5gag used to initiate the viral competition study. Last two lanes are passage 11 analysis of duplicate passages of the competition study (each virus at MOI 280 vp).

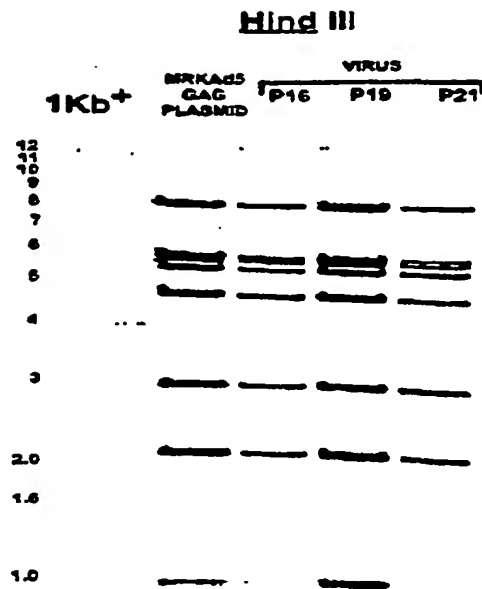
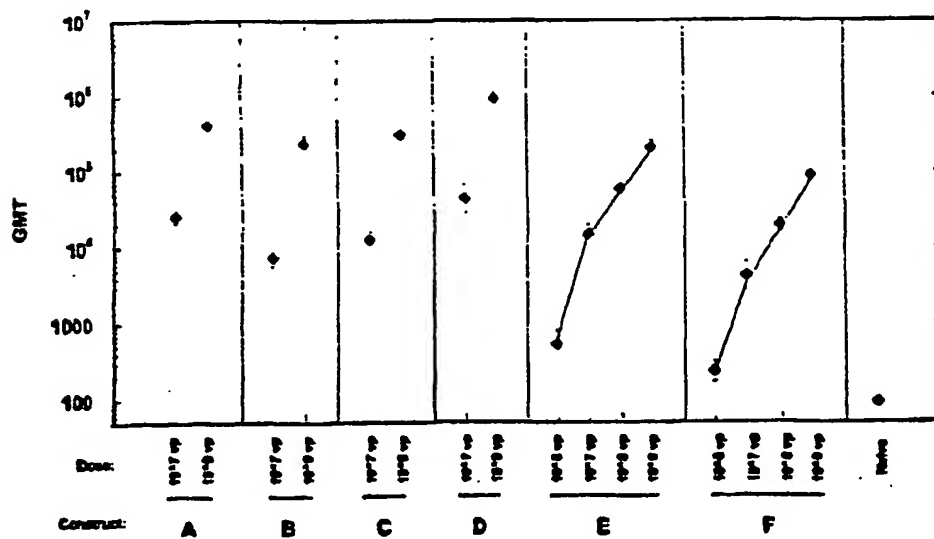


Figure 12: Viral DNA analysis by *Hind*III digestion on high passage numbers for MRKAd5gag in serum containing media with collections made at specified times. The first lane shows the 1 Kb DNA size marker. The other lanes represent pre-plasmid control (digested with *Pac*I and *Hind*III), and MRKAd5gag virus continually passaged to P16, P19 and P21 (serum containing media).

13
Figure 13. Serum anti-p24 Levels at 3 Wks post i.m. immunization of balb/c mice (n=10) with Varying Doses of Several Adgag constructs: (A) MRKAd5gag (through passage 5); (B) MRKAd5 E3⁺ bCMV-FLgag-bGHpA; (C) MRKAd5 E3⁺ bCMV-FLgag-SPA; (D) MRKAd5 E3⁺ mCMV-FLgag-bGHpA; (E) research Lot (293 cell-derived) of Ad5HIV-1gag; and (F) clinical lot (Ad5gagFN0001) of Ad5HIV-1gag. Reported are the geometric mean titers (GMT) for each cohort.



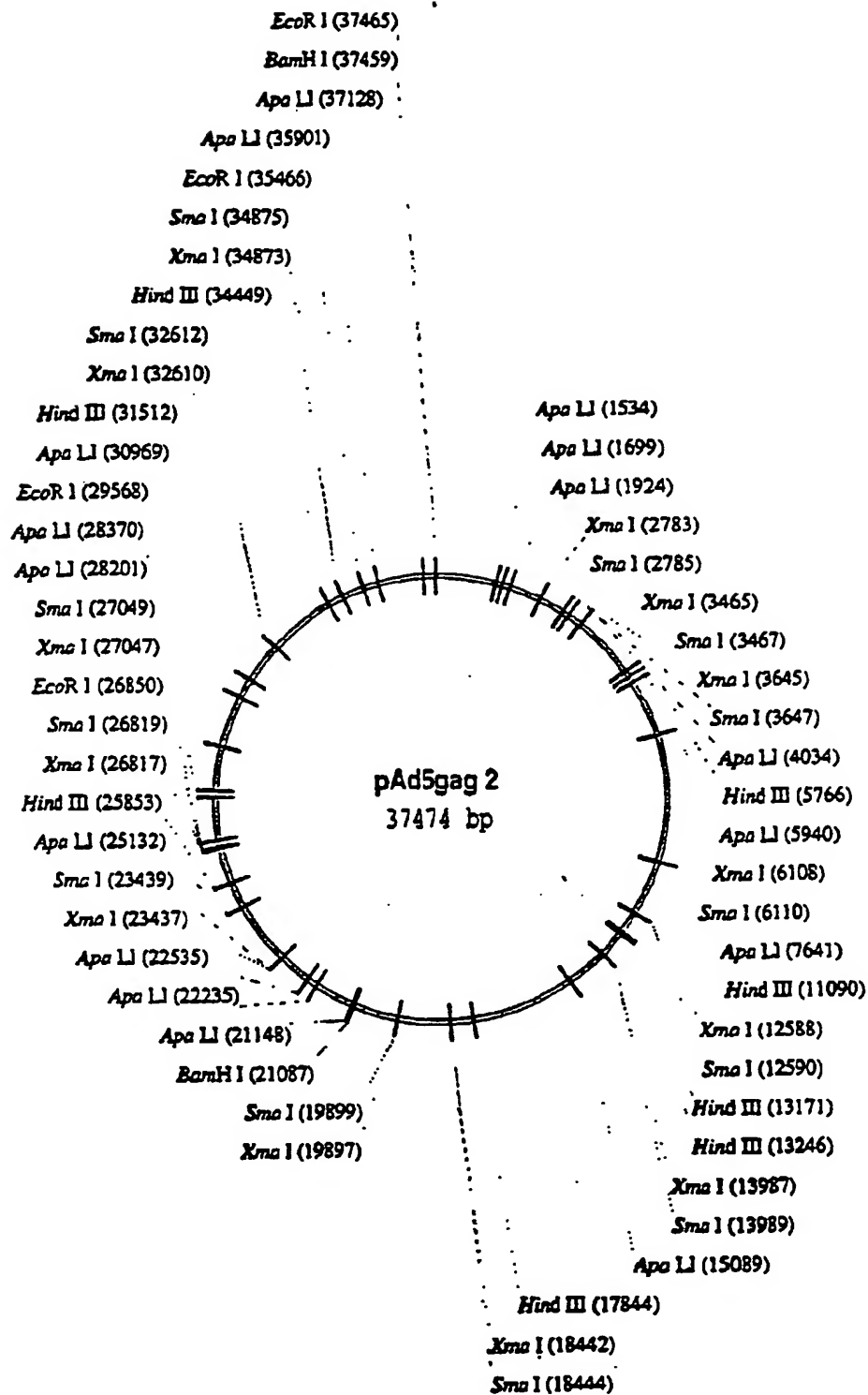


Figure 14

pMRKad5qay MER602

1	TTCTTAATTA ACATCATCAA TAATATATCT TATTTTGAT TAAATGAAAT ATGATAATGA GATATATGAG TTTTGTACCT GGGTGGGAC GATGGATGCT
101	AGAAATTAAT TGTAGTAGTT ATATATATGA ATAAATCTTA ATTTTGTAT TATTTATCT CTCCACCTC AACACTGCA CACCTTTCTT
201	GGGGGGTAC GTATGATGCT GGGGTAATG GGGGTAATG TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA
301	GGGGGGTAC GTATGATGCT GGGGTAATG GGGGTAATG TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA
401	GGGGGGTAC GTATGATGCT GGGGTAATG GGGGTAATG TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA
501	GGGGGGTAC GTATGATGCT GGGGTAATG GGGGTAATG TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA
601	GGGGGGTAC GTATGATGCT GGGGTAATG GGGGTAATG TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA
701	GGGGGGTAC GTATGATGCT GGGGTAATG GGGGTAATG TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA
801	GGGGGGTAC GTATGATGCT GGGGTAATG GGGGTAATG TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA
901	GGGGGGTAC GTATGATGCT GGGGTAATG GGGGTAATG TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA
1001	GGGGGGTAC GTATGATGCT GGGGTAATG GGGGTAATG TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA
1101	GGGGGGTAC GTATGATGCT GGGGTAATG GGGGTAATG TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA
1201	GGGGGGTAC GTATGATGCT GGGGTAATG GGGGTAATG TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA
1301	GGGGGGTAC GTATGATGCT GGGGTAATG GGGGTAATG TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA
1401	GGGGGGTAC GTATGATGCT GGGGTAATG GGGGTAATG TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA
1501	GGGGGGTAC GTATGATGCT GGGGTAATG GGGGTAATG TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA
1601	GGGGGGTAC GTATGATGCT GGGGTAATG GGGGTAATG TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA TGAATATGTA

Figure 15A

pMRKAI1:gen MER682

1701	CACCAAGGCA	TCTCCGCGCG	GACCTTAAAT	GCCTTAAAT	AGGATGAGGC	TCTCCGCGCG	AGGATGAGGC	CATCTCTCT	GCCTTCTCT
1801	AGGATGAGGC	AGGATGAGGC	CTGATGAGGC	CTGATGAGGC	CTGATGAGGC	CTGATGAGGC	CTGATGAGGC	CTGATGAGGC	CTGATGAGGC
1901	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC
2001	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC
2101	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC
2201	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC
2301	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC
2401	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC
2501	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC
2601	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC
2701	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC
2801	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC
2901	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC
3001	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC
3101	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC
3201	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC	AGGATGAGGC

Figure 15B

[illegible]

21/144

pMRKad5gag MER6R2

6501 GCGTCACGCA CGAAGGAGCG GTAGGAGTGG CCGAGCTGTT TGAATAGATT GAGGATGATC TGCAGCTCTA GAGGAGGATG GTCCAGGATT TCCCTGATGA
 6601 CCGAGTGGCT GCTTCTCTCG CATCTTCAGC GGTGTCAGCA ACTGATGAGG CCGTACTGAT CCGGCTGAT CCGGCTGAT CAGGTGCCAA AGGAGTACT
 6701 TGTGATATCT ATCTGCTGCG TTTTCTTTC ACAGCTGATG GTTGAATGTA AATCTTCTG GATCTCTTCA GTACTCTTGG CTTCTGCTCT
 6801 ACAGTATGAA TAGGACAGCG AAAAAAAGG TGTGAGTGC CACTCTCTT TTTGAGGAGG CCGAGGAGGT CAGTGAAGCC TAGGCTTTGG GCAAGCTGAG
 6901 GAGAGGTGAA GAGCTTAGCA GTTAGAGTGG GTTAGAGTGC TGTAGAGTGC AATATCTCT TTTTACTGAT AGGCTGATG CTTCTGCTGAG GAGGCTGATG
 7001 GCTTGGCAAT CTGAGATCTT ACATCTTAC CACTGCGCG ACATCTCTG TTTTATGAGG TCTGATGAGG CCGGATGAG GAGGCTGATG AGGCTGATG
 7101 CTTGACAGCG ACTGCGTTT CACAGGAGC TGTACTGAA ACTTATGAG CATTATGAGG TTTTCTGAGG AATATGAGG GAGGCTGATG AGGCTGATG
 7201 CCGTGGCTT TTTGAGAGC GATTTGCGA GGGGAGAGT CCGGCTTCCA CTTTATGAGG TTTTCTGAGG AATATGAGG GAGGCTGATG AGGCTGATG
 7301 GGCACCGGAA AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG
 7401 TCCCGGAGC TCGGAGAGC AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG
 7501 GAGGAGGCTT TGTGAGAGC AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG
 7601 GAGGAGGCTT TGTGAGAGC AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG
 7701 GAGGAGGCTT TGTGAGAGC AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG
 7801 GAGGAGGCTT TGTGAGAGC AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG
 7901 GAGGAGGCTT TGTGAGAGC AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG
 8001 GAGGAGGCTT TGTGAGAGC AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG AAGCTTTGCG

PMKACI59a9 MF:R602

[illegible]

PHKRad'stag MER6B2

12901	GGATGATATG CCTCANNCCG GCGCTTTATC AACCTCTTAA TTAATCTACTT GATTTCTCTG GCGCTCTCTA ACCCTCAAT TTTACCAAT GCTATCTTCA
13001	CGGTACATAC GGAGTTTGGC CGGCAATAG TTTATTAAT ACCATATGAA CTAATCTATC CAGCTCTAT TATGACTCAT AAATGCTTA CTAATCAAT
13101	ACCGCACTG GCTACCTGCG CCGCTCTCTT ACACCTCTCTT ATTCGATCTG CTTATATGTA ACATATAT TCTCTCTGAC GACATAGACG ACATCTCTGTT
13201	TGCGCTGAC CGATGCGCGG GACCAAAAG TTTTCTCTCT TAAGCTCTAC GATTTCTCTA TGTATCTTAA GAGAGCTCTG CTCTATCTG TGTCTCTCTA
13301	TTCTCTCTAA CGCGACCTCC TCTATAGATT GTACATCTCT GAGCTCTCTG AGCTCTCTCT TCTCTCTCTA GCGCTCTCTA GCGCTCTCTA
13401	AAAGGCTCTT GCGCTCTCTA ACATCTCTA GCGCTCTCTA GCGCTCTCTA GCGCTCTCTA GCGCTCTCTA GCGCTCTCTA GCGCTCTCTA
13501	CTAGGCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG
13601	GAATCTCTAC GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG
13701	AAATCTCTAC GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG
13801	CTAGGCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG
13901	GAATCTCTAC GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG
14001	CTAGGCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG
14101	GAATCTCTAC GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG
14201	CTAGGCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG
14301	GAATCTCTAC GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG
14401	CTAGGCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG GCGCTCTCTG

Figure 15I

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17601	TCGACACACG	CATATATGAC	GTTGAGGCT	TCAGCTGAGG	CTTGTGTTG	ATGTAATGTA	AAATTTTAT	TTCACCTTT	AAATATATG	GCAGTACG
17701	AGCCCTGCT	GTTATATG	CCACCCGCG	ATGTCAGCT	GAGGACATC	TTCCTGTAAT	TTTAAATAC	AGCTGACG	TTCTGATAC	CGTCTGCT
17801	CTGACACACG	AGCACAGCT	AGATGCTG	AGATGCTG	AGATGCTG	AAATGTAAT	AAATGTAAT	AAATGTAAT	AAATGTAAT	AAATGTAAT
17901	GACCTGCTG	TGCTGCTG	TCATGCTG	TCATGCTG	TCATGCTG	TCATGCTG	TCATGCTG	TCATGCTG	TCATGCTG	TCATGCTG
18001	CTGACACACG	AGCACAGCT	AGATGCTG	AGATGCTG	AGATGCTG	AAATGTAAT	AAATGTAAT	AAATGTAAT	AAATGTAAT	AAATGTAAT
18101	TCGACACACG	CATATATGAC	GTTGAGGCT	TCAGCTGAGG	CTTGTGTTG	ATGTAATGTA	AAATTTTAT	TTCACCTTT	AAATATATG	GCAGTACG
18201	AGCCCTGCT	GTTATATG	CCACCCGCG	ATGTCAGCT	GAGGACATC	TTCCTGTAAT	TTTAAATAC	AGCTGACG	TTCTGATAC	CGTCTGCT
18301	CTGACACACG	AGCACAGCT	AGATGCTG	AGATGCTG	AGATGCTG	AAATGTAAT	AAATGTAAT	AAATGTAAT	AAATGTAAT	AAATGTAAT
18401	GACCTGCTG	TGCTGCTG	TCATGCTG	TCATGCTG	TCATGCTG	TCATGCTG	TCATGCTG	TCATGCTG	TCATGCTG	TCATGCTG
18501	CTGACACACG	AGCACAGCT	AGATGCTG	AGATGCTG	AGATGCTG	AAATGTAAT	AAATGTAAT	AAATGTAAT	AAATGTAAT	AAATGTAAT
18601	TCGACACACG	CATATATGAC	GTTGAGGCT	TCAGCTGAGG	CTTGTGTTG	ATGTAATGTA	AAATTTTAT	TTCACCTTT	AAATATATG	GCAGTACG
18701	AGCCCTGCT	GTTATATG	CCACCCGCG	ATGTCAGCT	GAGGACATC	TTCCTGTAAT	TTTAAATAC	AGCTGACG	TTCTGATAC	CGTCTGCT
18801	CTGACACACG	AGCACAGCT	AGATGCTG	AGATGCTG	AGATGCTG	AAATGTAAT	AAATGTAAT	AAATGTAAT	AAATGTAAT	AAATGTAAT
18901	GACCTGCTG	TGCTGCTG	TCATGCTG	TCATGCTG	TCATGCTG	TCATGCTG	TCATGCTG	TCATGCTG	TCATGCTG	TCATGCTG
19001	CTGACACACG	AGCACAGCT	AGATGCTG	AGATGCTG	AGATGCTG	AAATGTAAT	AAATGTAAT	AAATGTAAT	AAATGTAAT	AAATGTAAT
19101	TCGACACACG	CATATATGAC	GTTGAGGCT	TCAGCTGAGG	CTTGTGTTG	ATGTAATGTA	AAATTTTAT	TTCACCTTT	AAATATATG	GCAGTACG
19201	AGCCCTGCT	GTTATATG	CCACCCGCG	ATGTCAGCT	GAGGACATC	TTCCTGTAAT	TTTAAATAC	AGCTGACG	TTCTGATAC	CGTCTGCT

Figure 15L

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19301	AGAACTAAAG	GGCCACAAAT	CTATGTCAA	CAGGCTAAT	TACATGCTT	TACGCTAAT	TTTATTCCT	CTATGCTAT	ACACAGCAG	GGCTAATAT
19401	TCTTGATAC	CGGTTGTTA	GATACGGCT	TCTGCTAAT	ATGTAACGA	ATCTCTCTT	NAATACCA	GATTACATA	TGTTGCTG	CCCATTTAT
19501	GGTGTCTGG	GGGECANCC	ATCTGCTG	ATCTGCTG	TAGATTGCA	AGACAGAAC	ACAGAGCTT	CATACAGCT	TTTCTGCTG	TCCATTTGCT
19601	CCACAGACC	GGCCGGTTC	TAGGCTAAC	TAGGCTAAC	ATCTAACCT	TCCTCTCTT	TGCTCTGAA	GTATGCTGA	AAACAACTA	TCCATTTGCT
19701	ATAGAACCA	GTACTTTCT	ATGCTGCTG	ATGCTGCTG	CAGCTATAT	CCAGATTTA	GTATTTTAA	AAATGCTGA	ACTGAGATG	ACTTTCTGA
19801	TATCTGCTT	CATGAAAGA	TACACCTAG	TACACCTAG	TCCGACACT	CTTACCTAG	TAAACCTAA	GAATGCTGA	GGGAAAGGA	TGCTACAGAA
19901	ATACAGGAA	GGTACCCCT	CACACTAAT	ATGCTGCTG	GAATGCTG	GAATGCTG	ATTTGCTG	TTTATGCTG	CCCTTTCTT	ACGATGCTT
20001	TTTTCAGAT	AAATGAAAT	AGAGTTGTA	ATATTTTTC	CCATGAAAT	CAATGAAAT	CCATGAAAT	GGGAAATTT	CCCTGCTG	AACATGCTG
20101	AAAGTCTAT	TTTACTTTA	TTTCTAACC	TTTATTAAC	GGTACCTTA	GTATGCTTA	GTATGCTTA	CGCTGCTTA	CGCTGCTTA	TTTATGCTT
20201	TGTTATGCT	CGACAGCTA	AGTACAGTC	CTTCTGCTG	AAATTTCTT	AAATTTCTT	GAATGCTTA	ACACTGCTA	ACACTGCTA	TGCTGCTG
20301	ACATAAAGG	GGTCTGCTG	TTCTATGCT	TTCTATGCT	GAATGCTG	GAATGCTG	GAATGCTG	TGCTGCTG	TGCTGCTG	ACCTGCTG
20401	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG
20501	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG
20601	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG
20701	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG
20801	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG
20901	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG	GGTCTGCTG

Figure 15M

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21001	TTATTTCTAT	GGGGGACATC	ACAGACTTGG	CCCAAAACCT	TCCTTACTTC	AACTGCTGCT	ACGGCTACGA	CATGACTTTT	GGGTTGATTC	CCATGACATGA
21101	AAATACAGTA	CCCGGCTGAG	TGCTCTGACC	CGTTTCTGGA	ATAGATGATG	TTGAGATGAT	TTGGGATGAT	GTATCTGAAA	CTCCACCTAG	GGTACCTGCT
	GGCCACCTCT	CTTTATGTTT	TGTTGAGAT	CTTTGAGATG	GTCCGCTGAT	AGCAATGCTA	CTGCTGCTG	ATCCAAACCG	TGTACCTGCG	CAGGCTCT
	CGGCTGGGAA	GAATACAAA	ACAAACTTCA	GAATCTGAC	GAATCTGAC	GAATCTGAC	GAATCTGAC	TAGCTTTGGC	AC/TTGACGC	GTGCGGAA
										ηηηηηηηη
21201	TCGGCGGCA	ACGGCAGAC	ATTAAGAGC	ANGCAACATC	ANGCAACATC	ANGCAACATC	GGCGGCTG	GGCGGCTG	GGCGGCTG	TCAGAGATCT
21301	ATCGCGGCT	TGCGGCTG	TATTTCTT	TATTTCTT	TATTTCTT	TATTTCTT	GGCGGCTG	GGCGGCTG	GGCGGCTG	GGCGGCTG
21401	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG
21501	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG
21601	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG
										ηηηηηηηη
21701	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG
21801	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG
21901	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG
22001	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG
										ηηηηηηηη
22101	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG
22201	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG
22301	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG
22401	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG
										ηηηηηηηη
22501	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG	GGGATGCGG

Figure 15N

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22601	ATCTTGCCCT TCTAGACTG CTCTTTACG GCGCTATAC CTTTCTTCT (TTCACATCC ATTTCATTA CCGTCTCCCT ATTATCATTA ATGCTTCCCT TAGAACCGGA ACCATCTGAC GATGATATCG CCGGTGATCG CCGGTGATCG CCGGTGATCG TAAATAGTAT GCACGAGGGA TAAATAGTAT TAGGAGGGA Pall
22701	GTAGACACTT AAGCTGCGCT TCGATTTAG TCGATTTAG TCGATTTAG TCGATTTAG TCGATTTAG TCGATTTAG TCGATTTAG TCGATTTAG TCGATTTAG CATCTGTGAA TTGAGAGCGGA AGCTAGACTG GCGTCCGAC GTTCTCTTC CCGTCTCTTC CCGTCTCTTC CCGTCTCTTC CCGTCTCTTC CCGTCTCTTC Pall
22801	CAGGTACGCT TCGAGGAAAT GCGGATCAT GCGGATCAT GCGGATCAT GCGGATCAT GCGGATCAT GCGGATCAT GCGGATCAT GCGGATCAT GTCCATGCGG ACCTGCTTAG CCGGTAGTA CCGGTAGTA CCGGTAGTA CCGGTAGTA CCGGTAGTA CCGGTAGTA CCGGTAGTA CCGGTAGTA Pall
22901	CATACGCGCG CCGAGACTTC CACTGCTCA CCGAGTAGT TTAAGTTTC CTTTATGATG TTAATTCAGT GTTACTTGTG CATACGCGCG CCGAGACTTC GTATGCGCGC GGTCTCGAAG GTGATGCAAT CCGTATGCA ACTTCATGCG GAAATCTAGC AATAGGTGCA CCGTATGCA GTTACTTGTG CCGAGACTTC Pall
23001	CCATGCGCTT CTGCAACGGA GAGAGGATCG GAGAGGATCG GAGAGGATCG GAGAGGATCG GAGAGGATCG GAGAGGATCG GAGAGGATCG GAGAGGATCG GTATGCGCGC GAGAGGATCG GAGAGGATCG GAGAGGATCG GAGAGGATCG GAGAGGATCG GAGAGGATCG GAGAGGATCG GAGAGGATCG GAGAGGATCG Pall
23101	CCGATTAACCA CCGGCTACTG GATGCTCTTC ATTGAGTGC TCGACTTTC GCTTACCTCC TTATGCTATC TTATGCTATC TTATGCTATC TTATGCTATC GCGGTATGCT CCGGCTACTG GATGCTCTTC ATTGAGTGC TCGACTTTC GCTTACCTCC TTATGCTATC TTATGCTATC TTATGCTATC TTATGCTATC Pall
23201	ACCATTTGTA GCGGCTACTG GATGCTCTTC ATTGAGTGC TCGACTTTC GCTTACCTCC TTATGCTATC TTATGCTATC TTATGCTATC TTATGCTATC TGTATGCTAT GCGGCTACTG GATGCTCTTC ATTGAGTGC TCGACTTTC GCTTACCTCC TTATGCTATC TTATGCTATC TTATGCTATC TTATGCTATC Pall
23301	TCCTGCGCGC AATGCGGAAA TCGGCGCGCG AATGCGGAAA TCGGCGCGCG AATGCGGAAA TCGGCGCGCG AATGCGGAAA TCGGCGCGCG AATGCGGAAA AATGCGGAAA TCGGCGCGCG AATGCGGAAA TCGGCGCGCG AATGCGGAAA TCGGCGCGCG AATGCGGAAA TCGGCGCGCG AATGCGGAAA TCGGCGCGCG Pall
23401	CTGATTAACG CCGGCTACTG GATGCTCTTC ATTGAGTGC TCGACTTTC GCTTACCTCC TTATGCTATC TTATGCTATC TTATGCTATC TTATGCTATC GATGCTACTG CCGGCTACTG GATGCTCTTC ATTGAGTGC TCGACTTTC GCTTACCTCC TTATGCTATC TTATGCTATC TTATGCTATC TTATGCTATC Pall
23501	GCACCGCTC CCGGCTACTG GATGCTCTTC ATTGAGTGC TCGACTTTC GCTTACCTCC TTATGCTATC TTATGCTATC TTATGCTATC TTATGCTATC CGTGGCGCAG CCGGCTACTG GATGCTCTTC ATTGAGTGC TCGACTTTC GCTTACCTCC TTATGCTATC TTATGCTATC TTATGCTATC TTATGCTATC Pall
23601	AGAGGAGCAG CCGGCTACTG GATGCTCTTC ATTGAGTGC TCGACTTTC GCTTACCTCC TTATGCTATC TTATGCTATC TTATGCTATC TTATGCTATC TCTTCTCTTC CCGGCTACTG GATGCTCTTC ATTGAGTGC TCGACTTTC GCTTACCTCC TTATGCTATC TTATGCTATC TTATGCTATC TTATGCTATC Pall
23701	GGAGGAGGGA GTGATTAACG AGCAGGACCC AGCAGGACCC AGCAGGACCC AGCAGGACCC AGCAGGACCC AGCAGGACCC AGCAGGACCC AGCAGGACCC CCCTCTCTCT CACTAATAGC TCGTCTCTCG TCGTCTCTCG TCGTCTCTCG TCGTCTCTCG TCGTCTCTCG TCGTCTCTCG TCGTCTCTCG TCGTCTCTCG Pall
23801	GCAGAGGCA ACAGAGGCA AGTGGCGCG AGTGGCGCG AGTGGCGCG AGTGGCGCG AGTGGCGCG AGTGGCGCG AGTGGCGCG AGTGGCGCG CTCTCTCTCT TCGTCTCTCT TCGTCTCTCT TCGTCTCTCT TCGTCTCTCT TCGTCTCTCT TCGTCTCTCT TCGTCTCTCT TCGTCTCTCT TCGTCTCTCT Pall
23901	CGGCAATAT CTGCGAGCGG TTGCGAGCGG TTGCGAGCGG TTGCGAGCGG TTGCGAGCGG TTGCGAGCGG TTGCGAGCGG TTGCGAGCGG TTGCGAGCGG CGGCAATAT CTGCGAGCGG TTGCGAGCGG TTGCGAGCGG TTGCGAGCGG TTGCGAGCGG TTGCGAGCGG TTGCGAGCGG TTGCGAGCGG TTGCGAGCGG Pall
24001	ACCGGCGGAA CCGGAGGAAA ACCGAGCAT ACCGAGCAT ACCGAGCAT ACCGAGCAT ACCGAGCAT ACCGAGCAT ACCGAGCAT ACCGAGCAT TGGGCGGCTT GCGGCTCTTT TCGGCTCTTT TCGGCTCTTT TCGGCTCTTT TCGGCTCTTT TCGGCTCTTT TCGGCTCTTT TCGGCTCTTT TCGGCTCTTT Pall
24101	TTTTTCCAAA ACTGCAAGAT ACCCTATTC TCGTCTCTCG ACCGAGCAT ACCGAGCAT ACCGAGCAT ACCGAGCAT ACCGAGCAT ACCGAGCAT AAGAGGCTT TCGCTCTCT TCGCTCTCT TCGCTCTCT TCGCTCTCT TCGCTCTCT TCGCTCTCT TCGCTCTCT TCGCTCTCT TCGCTCTCT Pall

Figure 150

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27301	CCCTCCGCGCC	ACTATCCCGGA	TCGAATTTAAT	CTTACCTTTC	ACGCTGTAAA	GGACTGCGG	GACGCTACG	ACTGAATGTT	AAGTGCAGAG	GCAGAGCAAC
27401	GGAGGCGCGG	TGATAGGCGT	AGTTAAATTA	GGATTGAGAC	TGCTCTAATT	CCTCAGCGCG	CTGCTATATC	TGACTTTACAA	TTTACCTCTC	CGTCTCTTTT
27501	TGCGCTGAAA	ACACTGCTC	CACCTGCTCT	GGCAGACTTC	CTTTGCTGCT	GACTTCGGTG	AGTTTTCCTA	CTTTGAAATG	CCGCAAGTATC	ATATCTGAGT
	ACCGGACTT	TGTGACACAG	GTGACAGCGG	CGGTGTTTAC	GAATGCTGCG	CTGACGCGAC	CTGACGCGAC	GAACCTTAAAC	GGGCTCTCTAG	TATAGCTCTT
	CCCGCGGCAC	GGCTGCGCGC	TTACCGCGCA	GGGAGAGCTT	GGCTGTAGTC	TGATTGCGGA	GTTTACCGAG	CGCGCGCTGC	TAGTTGCGCG	GGCAGCGGTA
	GGCGCGCGTG	CGCGAGGCGG	AATGCGCGGT	CCCTCTCGAA	CGCGCATGCG	ACTTAAGGCTT	CAATGCGGTC	CGCGCGCGAG	ATCAACTGCG	CGTGTGCGG
27601	CCCTGTGCTC	TCACTGTGAT	TTCGACTGT	CCTAAGCGTG	GAATACATCA	AGATCTTTGT	TGCAATCTCT	GTGCTCTACTA	TAAATTAATAC	AGAAATTAATA
27701	GGGACAGCAG	AGTGACACTA	AACGTTTACA	GGATTGCGAC	CTAATTTAGT	TCTAGAACCA	ACGGTAGAGA	CACGCTCAT	ATTATTTATG	TCTTTAATTT
27801	ATATACCTGCG	GCCTCTATCG	CCATCTGTA	AACGTCACCG	TTTTCACCGG	CCCAAGCAGAA	CCCAAGCAGAA	CCTTACCTCG	TACTTTTAAAC	ATCTCTCG
27901	TATATGACCC	CGAGGATAGC	GGTAGGACAT	TTCGCTGCG	AGGAGTGGG	GGTTTCGTTT	GGTTTCGTTT	GGATGCGACC	ATGAAATTTG	TAGAGAGGTA
28001	CTGTGATTTA	CAACAGTTTC	AACGAGACG	GAATGAGTCT	ACTAGAGAAC	CTCTCCGCGC	TCAGCTACTC	CATCAGAGAA	AACACGACCC	TCTTTACCTTT
	GCACACTAAAT	GTGTTCAAG	TGCGCTGCG	CTCAGCTGAC	TGCTCTCTTG	GAGAGGCTCG	AGTCAATGAG	GTAGCTCTTT	TTGTGCTGCG	AGGATGAGAC
	CGCGGACGCT	ACGATGCGGT	CACCGCGCG	TTACACGACAC	CTACCGGCTG	ACCGTAAGCC	AGACTTTTTC	CGGACGAGCC	TCATTAATCTC	TGTTTACCAAT
	GGCGCTTCCA	TGCTCAGCGA	GTGCGCGCG	ACGTGCTGCG	GAATGCTGAG	TGCGATTTGCG	TCTGAAAGAG	GGCTGCTCTG	AGTTATTTAG	ACAAATGCTC
	AACAGGAGGT	GGCTTAGGA	AACGCTTAG	GTATTTAGGCG	AATGCTGAG	CTACTGTGCG	GTTTATGAC	ACTGACGCG	ACTGACGCG	CTATTTCTAAT
	TGTGCTCTCA	CTCGAATCTT	TTCGGAATCC	CATTAATCGCG	TTTCCGCGTC	GATGACAGCC	CAGATACTTG	TTAAGTTGCT	TGAGATGCGC	GATTAACATTT
28101	TCAGGTTTCT	CTAGAAATCG	GGTTGCGGTT	ATTCTCTGTC	TTGCTATCTT	ATTACTAACGC	TCTCTCTGCT	ATGCTCTGCT	ATGCTCTGCT	GGCTCTCTT
28201	AGTCCAAAGA	GATCTTAAGC	CCAAACCCCA	TAAGAGACAG	AACACTAGAG	GAATATAGAA	TATGATTTGCG	AGAGAGCGA	TTCCGAGCGG	CGGACGACAC
	TGCACATTTG	CATTTATTTG	CAGCTTTTGA	AACGCTGCG	TGCGCACCCA	AGATGATTTAG	GTACATTAATC	CTAGGTTTAC	TCAGCTCTGCG	GTACAGCTTCT
	ACGTGTAAAC	GTAAATTAACA	GTGGAAGAAAT	TTCGAGCGCC	AGCGTGTGCT	TCTACTAATC	CATGATTTAG	GATCCAAATG	AUTGCGAGAG	CAGTCTGCTT
28301	GGTACCACCC	AAAGGTGGA	TTTTAAGGAG	CCAGGCTGTA	AGTTTACATTT	CGCAGCTGAA	CGTAAATGCT	GCACCACTCT	TATAAATGCG	ACCACAGAT
28401	CCATGGTGCG	TTTTCCACCT	AAATTTCTCT	GGTCCGACAT	TACAAATGTA	GGCTGAGCTT	CGATTTACTCA	CGTGTGAGAG	ATATTTTACG	TGCTGTCTTT
	ATGAAAGCT	GCTTATTCGC	CACAAAGACA	AAATTTGCGA	GTATCTGTT	TATGCTATTT	TGCGGCGCG	TGACACTACA	GAGTATATATG	TTACAGTTTCT
	TACTTTTCCA	CGAATTAAGCG	GTGTTTTTGT	TTTAACCGTT	CATACGACAA	ATACGATANA	CGCTCGCTGC	ACTGTATATG	CTCATATTTAC	AATGTCAGAA
28501	CCAGGTAAG	AUTCATATAA	CTTTTATGTA	TACTTTTCCA	TTTTATGAAA	TGTCGACAT	TACCATGTAC	ATGAGCAAAAC	AGTATTAAGTT	GTGCGCGCCA
28601	GGTCCCATTT	TCAGTATTTT	GAATAATCAT	ATGAAAGGT	AAATATCTTT	ACAGGCTGTA	ATGCTATCATG	TACTCGTTTG	TCATATTTCA	CACCGGCGGT
	CAAAATTTG	TGGAAGACAC	TGCACTTTTC	TGCTGCACTG	CTATGCTAAT	TACAGTCTCT	GGTTTGTCT	GTACCTTACT	CTATATTTAA	TACAAAGACA
	GTTTTAAAC	ACCTTTTGTG	ACCGTAAG	AGGAGCTGAC	GATAGGATTA	ATGTCACGAG	CGAAACGAGA	CATGCGATGA	GATATATTTT	ATGTTTTCTT
28701	GAAGGAGCTT	TATTTGAGGA	AGCAATATTC	CTTAATTTAC	TAGTTTACAA	AGCTAATCTC	ACCACTAATC	GGCTTACTCG	CTGCTGCGAA	AGCAATTTTA
	CTGCTGCGAA	ATATCTCTT	TCTTTTACG	GAATTAATG	ATTCAAAGTT	TGCAATTAAC	TGCTGATTTA	CGAATGAGCG	GACCAACGTT	TTGTTTTTAT
28801	AAAGTTTAC	ATTATTAATTA	GAATAGGAT	TAAAGCGCG	GGTCAATCTC	TGCTAATAC	CATTCGCTG	AACAAATGAC	TCTATGTCG	ATATCTCTTA
	TTTTCATCTG	TAAATTAAT	CTTATCTTAA	ATTGCGCGCG	CCAGTAAGCG	ACGATTTATG	GTAAAGCGAG	TTGTTAATCG	AGATTAACCG	TATACGAGTT

Figure 1SR

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28901 GGCCTACAC CTTGAGTCA GGTTCCTTA ATGTACAT CTGACTTGG CCAAGACTG TCCCTGGAT TTGTTCCAGT CCAACTACAG CCAACCCAGC
 CCGATCTTG GAATTCAGT CCGAAGGAT TACAGTCTTA GACTCAAC C GGTCTGTAC AGGCTGCTA AACAGGTCA GGTTCATGTC GCTTATAT
 29001 TAAAGAGAT GACCAACAC ACCAAGCTG CCGCTGCTAC CCACTTACA TTACACCA ATACACCCA ACTTCTGCC TTATCAATA ACTTGGATTA
 ATTCTCTTA CTGCTGTGT TGTGTCGCC GCTGCGATG GCTCAATCT AGATATCTT TATGTGGAT TCANAGAGG AACAGTAT TCAACCTAT
 29101 CTTGCGATG TGTGCTCT CCAATGCTT TATGTTTGA TGTCTTATA TTATGTTAT CATCTCTGC CTAAAGCCA AACGCGCCG ACCACCCATC
 GAACCGATAC ACCACCAAGA GGTATGCGA ATACAAAT ACCGAATAT ATACATCTA ATACATCTA TACAGTATG TACAGTATG TCAATGATG
 29201 TATATGCCA TCAATGCTT ACACCCAAAC AATATGTA TGTATAGAT GAGCGATG AACACATAT TCTTTCTCT TACAGTATG TCAATGATG
 ATATACAGGT AGTACACGA TGTGCTTGT TACTATCTT AGTATCTTA CCTGCTCTAC TTGTTGACA AGAAAGAGA ATGTCATCT AATTTACTT
 29301 CAGGATCTT CAGATTTTA TATTACTGAC CTTGCTGCG CTTTCTGCG ATTGCTGCG GTTCTGACA TCGAAGTGA CTGATTC A CTGATTC A
 GTACTAAGGA GCTCAAAAT ATATGACTG GGAACAGCC GAACAGAC GCAACATCT TACCGAGCC CAAGAGTGT ACCTTCATCT GACOTAGT
 29401 GCTTCACAG TCTATTTCT TTACGATTT CTACCCCTA CCTCTATCT GAGCTCATC ACTGCTGTA TCGCTTTAT CCACTGAT CACTGCTT
 CCGAGTCTC AGATTAAGGA AATGCTTAA CAGTGGAT GCGATGAC GTCATGATG TCACACCAT AGCGAATA GGTACGTTA CTGACCCATA
 29501 GTGCTGCTT TGCATATCT AGACACCAT CCACTACAG GACAGACT ATAGCTGAC TTCTTACAT TCTTTAATA TGAATTTAC TGTGCTT
 CACAGCGGA AGTATAGAG TCTGCTGAG GGTCTATCT CCTGCTCTA TATGACTG AGATCTTA AGAATTAAT ACTTTAATG ACATGANA
 29601 CTGCTGATA TTGACACCT ATCTGCTTT TGTGCTGGA CTTCCAGCC TCMAAGAT ATATCAAGCA GATTCACCTG TATATGAT ATTCAGAT
 GACGATAT AACCTGGA TAGAGCGAA ACAGGCTG GAGCTGCG AGTTCTGTA TATAGTACT CTNAGTACG ATATACCTTA TAACTTCA
 29701 GCTACATGA AAGAGCAT CTTTCCGAG CTTGCTTATA TCGATCAT TCTGCTGAG TACCATCTA GCGCTGCTA TATATCC A
 CATGTTACT TTTTGGCTA GAAAGCTTC GACCAATAT AGTTAGTAG AGACAATAC ACAGAGCTC ATGTAGAT CCGATGCT ATATAGCAT
 29801 CTTGACAT GCTGAGAG CATGATGC CATGATCC CCACTTTCC CCGGCTGCG TATGCTTCA CTGCAACAG TTGTTGCGG CCGCTTCTC
 GCACTGTA CCGACCTTC GTTATCTAG GTACTTGTG GTTGAAGG GCGCGGCG ATACGAGGT GACTTGTTC AACAGCGCC GCGGANA
 29901 CCAAGCAT AGCTGCGC ACTTCTGC ACCGACTG AATCAGCTA CTTTATCTA ACAGAGGAG ATGACTGACA CCGTATGCT AGAATGAC
 GGTGCTTAG TCGAGCGCG TCGAGAGCG TGTGCTGCTC TACTACTGT TACTACTGT GGTATCTA TCTTACTG
 30001 GCAATTTTA CAGAGCGCG CTTGCTGAG AGAGCGCG CAGCGCGA TGTATCTAG ATGATCTAG AGTCTCAGG CATGTTTAC TCGACCAT
 CTTAATAT GTCTGCTGC GAGGATCTT TCTGCTGCC GTGCGGCT GTTCTGCG TACTTACT TCGAGTCT CTACCAATG AACCTGCTA
 30101 GCAAGCGG TATCTTTT CTGCTGAG AGGCAAGT CACTTACAC AGTATCTA CCGGACAG CCGTACTAC CCGTACTAC CCAAGCTT
 CTTTCTCC ATAGAAACA GAGCTTTCT TCGCTTCT TCAATATGT GCGCTGCG GATATGAT TTCACCGCTT GGTATCTAT
 30201 GAAATGCT GTATGCTG GAGAAAGCC CATTTACATA ACTGACTG CTATGATG ATTCACAC CCGTACTAC CCGTACTAC
 CTTTACCC CAGTACACC CTCTTTTCTG GTATGCTAT TGAATCTA GCTCTCTG GCTTCCGCG TATGATGAG GACAGTCTC TCGACTCTA
 30301 CTCTCACCC TTATTAGAC CTTGCTGCT CTCAAGAT TTTTCTCT TACTATTA TAAAGTCA TAAAGTCA CTTACTTAA ATCAGTATG
 GAGAGCTG ATATATCTG GAGACCGCA GAGTCTCTAG ATATAGTAT TTTTCTCT ATTCGTAGT GATGATTTT TACTCATG

Figure 155

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30401	AAATTTCTGT	CAAGTATAT	CAGCAGCACC	TCCCTGCTCT	CCTTCAGACT	CTGTATTATG	AGCTTCCTCC	TGCTGCGAAA	CTTCTCCAC	ATCTAAATG
30501	TTTAAAGACA	GGTCANATTA	GTCTGCTGTG	AGCAACCGGA	GAAGATCGGA	GACTATNAGG	TTGAGGAGGG	ACCGACGTTT	GAAGAGGTG	TTACATTTTAC
30601	GAATGTCAGT	TTCTCTCTGT	TCCCTGCTCT	CCGTACCCAC	TATCTTCATG	TTCTTTATGA	TGAGCTGCTG	AGACCGCTCT	GAAGATACCT	TCACCCCTCT
	CTTACAGTCA	AGGAGGACA	AGGACAGGTA	GAAGTATATG	ATAGAAATAG	ACAAGCTTCT	ACTTCTGCTG	TTCTGCGAGA	CTTCTATGGA	AGTTGCTGTA
	GTATCCATAT	GAACAGGAAA	CCGTGCTCTC	AACTGCTCTC	TTCTTACTCT	CTCCCTTTCT	ATCTCCCAAT	GGGTTCAGAG	AGATTCCTCC	TGGGTACT :
	CATAGATATA	CTGTGCTCTT	GGCAGGAGG	TTGACACGGA	AAAGAAATAG	GAGGAAACA	TAGGGGTTTA	CCCAAAATTC	TCTCAGGGGG	ACCCCATAGAG
30701	TCCTTGCGCC	TATCGGACC	TCATGTTTACC	TCCATGCGCA	TGCTTGCTCT	CANAAATGAG	AACTGCTCTCT	CTCTGAGGGA	GGCGGCGAAC	CTTACCTCTCT
	AGAAAGCGGG	ATAGGCTTGG	AGATCANATG	AGCTTACCTG	AGTACCGCTA	GTCTTACCGG	TTGCGCGAGA	GAGACCTGCT	CCGCGCTTGG	GAATGAGAG
30801	AAATGCTTAC	CACTGTGAGC	CGACCTCTCA	AAANACCTAA	GTAAATATA	AACTGAGAAA	TATCTTACC	CCTCACAGTT	ACCTCAGAGG	CCCTTACCTCT
	TTTACATAG	GTACACTGCG	GTGCGAGAGT	TTTTTTGCTT	CAGTTTGTAT	TTGACCTTTT	ATAGACGTGG	GGAGTGTCAA	TGAGTCTTTC	GGATATGACA
30901	GGCTGCGGCC	GCACCTCTAA	TGCTGCGGG	GAACACTCTC	ACCTGCTAAT	CACAGGCCCC	CTTAACCGTG	CAGGACTCCA	AACTTAGCAT	TGCCACCCAA
	CCGACGCGGG	CGTGAGATT	ACCAGCGCCC	GTGCTGTGAG	TGCTACGTTA	GTGCTCGGGG	CGATGCGCAC	GTGCTGAGGT	TTGATCGTA	ACGCTGCTT
31001	GGACCCCTCA	CAGTGTGAGA	AGGAAGCTA	GGCTGCGAAA	CATCAGCCCC	CTTCACCCAC	ACCGATAGCA	GTACCTCTTAC	TATCACTGCC	TCACCCCTCT
	CTGCGGAGCT	GTACAGCTCT	TCTTTTGGAT	CGGAGCGTTT	GTAGTCTGGG	GGAGTGGTGG	TGCTATCTCT	CATGCGAATG	ATAGTACCGG	AGTGGCGGAA
31101	TAACTACTGC	CACTGTGAGC	TTGCGCATTG	ACTGTAAAGA	GCCTATTTAT	ACACAAATAG	GAANACTAGG	ACTAAAGTAC	GGGCTCTCTT	TGCTGTTA
	ATTGATGAGG	GTGACCATCG	AACTGTTTCT	CGGTAAATTA	TGCTTTTATC	TGCTTTTATC	CTTGTGATCC	TGATTTCTAG	CCCCGAGGAA	ACCTACATTT
31201	AGAGGACTTA	AACACTTTGA	CGGTAGCAAC	TGCTGCGAGT	GTGCTATTTA	ATAATCTTCT	CTTGCMAACT	AAAGTACTGG	GAAGCTTGGG	TTTTGATTTCA
	TCTGCTGAGT	TTGTGAACT	GGCATCTTTG	ACGAGTCTTA	CACGTATTAAT	TATTATGAG	GAAGCTTTGA	TTTCAATGAC	CTGGGAGGCC	ANAACTAA
31301	CAGGCAATTA	TGCACCTTAA	TGTAGCAGGA	GGACTAAGTA	TGATTTCTCA	AAACAGAGCC	CTTATACTTG	ATGTTAGTTA	TCCGTTTGGT	GGCTCAAACT
	GTCTGCTTAT	AGTTGAAAT	ACATGCTCT	CTGTATTTCT	AACTAGAGT	TTTGTCTGCG	GAATATGAGC	TACATTCAT	AGGCAACTTA	CGATTTTCT
31401	AACTAAATCT	ANGACTAGGA	CAGGCGCTC	TTTTTATANA	CTCAGCCCC	AACTTGGATA	TTAACTAGAA	CANAGGCTCT	TACTTGTTTA	CAGCTTCAA
	TGATTTTAGA	TTCTGATCT	GTCCCGGGAG	AAATATTTT	GAAGTGGTGG	TTGAACTTAT	AACTGATGTT	GTCTTCCGAA	ATGAACTAAT	GTGCAAGTTT
31501	CANTTCCAAA	ANGCTTGAGG	TTAACTTAG	CAGTGGCAGG	GGTTGATGTT	TTGACCTTAC	AGCCTAGCC	ATTAAATGAG	GAATGCGCT	TGATTTGCT
	GTATAGGTTT	TTGCAACTCC	AACTGAGTTC	GTGAGCGTTC	CCCACTACA	CACTGCGATG	TGCTATGCG	TGATTTAGCTC	CTCTACCCGA	ACTTAAACCA
31601	TCAGCTAAATG	CAGCAACAC	AAATCCCTC	AAACANANA	TTTTCAGTGG	CCTAGAAATTT	GAATCAAGCA	AGCTATGCT	TCTTAACTTA	GGAACTGCTC
	AGTGGATTAC	GTGCTTTGTT	TTTGTGTTT	AACTGCTTAC	GGATCTTAAA	CTAGCTTTCT	TCCGATACCA	AGGATTTGAT	AGGATTTGAT	CCTTGAACCTG
31701	TTAGTTTGTGA	CAGCAGAGT	GGCATTTACG	TAGCAACGAA	AAATATGAT	AACTTAACTT	TTTTCACCC	ACCACTGCTA	TCTCTAACT	GTAGACTTAA
	AACTAAACT	GTGCTGTCCA	CGGTAAATGTC	ATCTTTGTT	TTTTTACTTA	TTCTATTGAA	ACACTGCTGG	TGCTGAGGT	AGAGGATGGA	CATCTGATTT
31801	TGCAGAGAAA	GAATCTTAAAC	TCACTTTGCT	TTTGTAGAAA	TGCTGAGTCT	AAATCTTCTC	TACACTTTCA	GTCTTGTGCTG	TTTAAAGCGAG	TTTGTGCTGCA
	ACGCTCTCTT	CTACGATTTG	AGTGAANCCA	GAATGTTT	ACAGCGTAC	TTTATGAGCG	ATGTCANAGT	CANAAACCGC	AAATTTCCCTC	AAACCGAGGT
31901	ATATCTGGA	CAGTTCAAGG	TGCTCATCTT	ATTATAGAT	TTGCGGAAA	TGAGTGTGCTA	CTAAACAAAT	CGTTCTGCTGA	CCCAATATAT	TA .AACTTTA
	TATAGACTCT	GTCAAGTTTC	ACGAGTAGAA	TATATTTCTA	AACTGCTTTT	ACCTCAAGAT	GAATTTGTTAA	GGAAAGGACT	GGTCTTTATA	ACCTTGAAT
32001	GAATGCGAAA	TCTTACTGAA	GGCAAGCTCT	ATACAAAGCG	TTTTGATTTT	ATGCTTAACT	TATCAGCTTTA	TCCAAATCT	CACGCTTAAA	CTGCCAAGAG
	CTTTACCTCT	AGATGACTT	CCGTGCTGGA	TATGTTTCTG	ACAACTTAAA	TAGCTGATGG	ATAGTGGAT	AGGTTTNGA	GTGCCATTTT	GAAGCTTTTC

Figure 15T

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32101 TAACATGTC AGTCAGTTT ACTTAACGG AGCAAAATCT AACCTGTGA CACTAACAT TACACTAAC GGTACACAGG AACACGAGA CACACTCTA
 32201 ATGTGAACAG TCAGTTTCAA TGAATTTTCC TCTGTTTTTA TTCTAACAT GGTATTTGTA ATGTATTTG CCATGTTTCC TTGTCTCTCT GTTGTGATG
 32301 AGTGCATACT CTATGTCATT TCTATGCGAC TATATCTGAT ACATATCAT TATATTAATA TTATCTACAT CTTCTTACAC TTCTTCATAC ATTGCCANV
 32401 TCACGATATGA GATACAGTAA AGTACCCCTG AGCAACCGGG TCTTATATTA ATTACTTTAT AACCTGTGA GGAAGATATG AAAGATATG TAACTGTCTT
 32501 AATAAGAAAT CGTTTGTGTT ATGTTTCMAC GTTGTATTTT TCAATTTGA GAAATTTGA ATCTATTTT CATTCAGTAG TATAGCCCC CACACTACATA
 32601 TTATTTCTTA GCACACAA TACAAATGG CACAAATAA AGTTAAGCT CTTTAAAGT TCAATTAATA GTAACTCAT ATATCGGGT TGTGTCTTA
 32701 GCTTATACAG ATCACCGTAC CTTATACAA CTCACAGAAC CTTAGTATTC AACCTTCAC CTCTCTCCA ACACACAGAG TACACAGTCC TTCTTCCV
 32801 CGAATATGTC TAGTGCATG GAATTAAGTT GATGTCTTGG GATCATTAAG TTGATCTGTO TTTGATCTG CAGCTAGGAT ATGTGTCAGG AAGAGGCG
 32901 GCTGGGCTTA AAAGCATCA TATCATGGGT AACAGACATA TTCTTNGTGT TTATATTTCA CACGTTTTC TGTCTGAGCA AACCTCATC AGTATATT
 33001 CGACCGGAAT TTTCGTAGT ATAGTACCCA TTGTCTGTAT AAGATCTCAC AATATAAGT GTGTCCAAAG ACAGCTCGGT TTCTGAGTAG TCACTATAV
 33101 ATAAACTGCC CGGCGAGCTC ACTTAAGTTC ATGTGCTGTT GTATATCTGT ACCCAGAGG TCTCTGTCCA CTGTGCTGTT GTTAACTGCG GTTAACTGTA
 33201 TATTTAGGCG GCGCGTGGAG TGAATTCAG TACAGCGACA GTTGAGCAC TGGGTCTGCG AGCAGAGGTT GAACGCGAAC GAATTCGCGG CGCTTTCTCT
 33301 AAGTCCAGCC CTACATGGGG GTAGAGTCAAT ATCTGTGAT CAGGATAGGG CGTTGTGCT GCAGAGGTC GCATTAACAC TGTCTGCGCC GCTCTCTGCT
 33401 TTCAAGTGGG GATGTACCCC CATCTCAGTA TTAGCACGTA GTCTATATCC TCCACACAGA GTCTGTGCGG CACTTATTGG ACUAGCGGCG CCGCGAGCCA
 33501 CCTGCAGGAA TACACATGG CAGTGTCTTC CTCAGGATG ATTGACAGG CCGGAGCAT AAGCTGCTT GTCTCTCGCG CACAGCAGCG CACCTGTAA
 33601 GAGCTGCTT ATGTTGTACC GTCAACGAG GAGTGGCTAC TAAGCTGTC GCGGTGCTA TTCTGCGCAA CAGAGGCGCC GTGTCTGCGC GTAGACTT
 33701 TCACCTTAAT CAGCAGAGTA ACTGCAGCAC AGCACCACAA TATTTTTCMA ATCTCCACAG TGTAAAGGCG TGTATGCGAA GCTCATGCGG GCGACACAG
 33801 AGTGAATTTA GTGTGTGCAT TGACGTCTGT TCCTGTGTTT ATACAAAGTT TTAGGCTGTC AGTTCCTCGG ACATAGGTTT CAGTATGCGC CCGTGTGTC
 33901 AACCCAGCTG GGCATCATAC CACAAAGGCA GTTAGATTAA GTTGCGTACC CTCATNAACA CTTCTGACAT AACATTAGC TCTTTTGCCA TTTTGTAAAT
 34001 TTGCTGTCAC CGTATGATG GTGTTGCGCT CCATCTAATT CACGCTGCG GAGTATTTGT GGTACCTGTA TTGTAAATGG AGAAGACGCT ACACATTAA
 34101 CACCACTGCC CGTACCATTA TAACTCTCTG ATTAACATG GCGCCATCCA CTACATCTCT AACCCAGCTG GCCAAGACT GCTCTGCGCC TATACACTT
 34201 GTGTGTGAGG GGCATGCTAT ATTTGGAGAC TAATTGTAT CCGGTAGCT GTGTGTAGGA TTCTGTGAG CCGTCTTGGT CCGCGGCGCG ATATGTGAG
 34301 AAGGAGCCCG GACTGTACCA ATGACAGTGG AGAGCCGAGG ACTGTAAAC ATGTATATC ATGTCTGTCA TGTATATCAAT GTTGTGACAA CACAGGACCA
 34401 TCGCTGTGCC CTGACCTTGT TACTGTACCC TCTCGGCTCC TGAGCATTGG TACCTAGTAG TACGAGCAT ACTATAGTTA CAACCTGTT GTGTCTGCT
 34501 COTGCTATCA CTCTCTCAGG ATTACAGCT CTCTCGCTGT TACAACTATA TCCCAAGGAA CAGCCATTC CTGATACAGC GTAAATGCG CACTTCAGCG
 34601 GACGATATGT GAGAGAGTCC TAATGTTCCA GAGAGGCGCA ATCTGTGAT AGCTGCTCTT GTTGTGTAGG GACTATGCT CATTTAGGCT GTAGCTCC
 34701 AAGAGCTGCG ACTTAAGTCA GGTGTGCTAT TCTTAAGTGG GTACATGCG GAGAGAGCT ATGATCTCTC GCGCTGTTTC CCGCTGCTCA TGTCTGTA
 34801 TTCTGTAGCG TGCATTGAGT GCACACGCTA ACATTTTAC AATGTAAAGC CTTCTGTGAC TACTATGAG TCTATCATC CCGCCCAAG ACAGAGTTT
 34901 GAGAGTACAG GATCTCTACT GTACGATATG GTCGATACCA ACCGAGATCG TTTGTGCTT ACTGTCTATC CAATGCGAAC GCGCGACGTA GTCATATT
 35001 CCTCCATCTG CTAGGATGCA CATCTCTCAC CGCTCTCTGT TGCTCTAGC ACACCAACA TCACAGTAGG GTTACTCTG CCGCTGCGAT CAGTATTAAT

Figure 15U

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33601	CTGAGCAGAA ACCAGGTGCG GCGGTACAA ACACATCTTC GTCTCTGCTC TTTCTGCTTA CACTCTCTTA
33701	GACTTCCTTT TGTTCACGCG CCGCACTTTT TGTCTAGACG CAGAGGTCAG ATGTCGCAAT CTATGAGAGT
33801	AAGCATCCAG GCGCGCCCTG GCTTCGCTTT CTATGTAATC TCTCTCTGCTT GCTCTCTGCTT GCTCTCTGCTT
	TTCTGAGGTC CCGCGCGGAC CGAAGCCCAA GATACATTTT AGCAATGACT CCGCGAGCGG ACTATTTGAG
	ACCTACACAT TCGTCTCTCG AGTCACACAC GCGAGTACCG GAGAGGCTG GAGACACCAT GTTTTCTTTT
	TGAGTGTGTA AGCAAGAGCG TCACTGTCTG CCGTCTCTCG CTTCTCTGTA CAAAGAGAAA ANTAGGTTT
33901	ATGAGAGTCT ATTANGTAA CCGCTCTCC TCGGTGAGG TGTCTMACT CTACAGCAA AGACAGATA
34001	TACTTCTAGA TAATTCATT CCGCGAGCG AGGCCAGCG ACTAGTTTGA GATGTCGCTT TCTGTCTAT
34101	TCCAAAGCG AAGCGGCTT CAGCTCCAG TCGAGCTTAA GGTAAATCCC TTCAGGTTGA ATCTCTCTTA
34201	AGGTTTCTCG TTGCGCGGGA GTGCGGCTT ACTGCAATT CCGATTTGCG AGTCCCACT TAGAGGAT
34301	ATAAATCTC ATCTCGGCAC TTCTCTAAT TAATCTTAAG CAAATCCGA ATATTAAGTC CCGGCAATG
	TTATTAGAG TAGAGCGGTG GAGAGTTAT ATGAGTTTC GTTTAGGCT TATATTTGAG GCGGTAACA
	CAGCTCAG CAGCGAATCA TGAATGCATA AATTCAGTT CTTCAAGAC CTGTATAGA TTCMAAGCG
	GTGCTCTTCT CAGGCTTACT ACTAACCTT TTNAGTCAA GAGTGTCTG GACATATTTT AATTTTCTG
	GTGCTCTTCT CAGGCTTACT TGAACATAT COTGCAATC TGCAGGAC AGCGCGGCA CTTCCCGCG
	CCAGCGAGCG GTGCGGCTG ACTTGATTA GCACTTCCAG ACOTGCTCG TCGCGCGGT GAGGCGCGG
34401	TATGACAGC ATACTCGAG CTATGCTAAC CAGGTAGCC CCGATGTAAG CTGTGTCAT GGGCGCGAT
34501	ATACTGTGCG TATGAGCTC GATAGGATG GTGCAATCG GTTACATTC GACMACGTA CCGCGCGCTA
34601	GCGAAGGCT CCGCGAATA AGAAGCACA TGTATGCTAT GTTATGCTAG ATAAAGCAG GTAAAGTCCG
	CGGTTTCCGA GCGGCTTTT TCTTCTGCT AGCATCAGTA CGATGCTC TATTTCCGTC CATTCGAGCG
	TCTCAACAT GTCTCGGCT TTCTGCTAA ACACAAATA ANATAACAA AATACATTA ACATTAAGA
	AGATTGTA CAGACGCCA AGACGTAAT TGTGTTTAT TTATTTGTT TTGTATTAAT TGTATATCTT
34701	ATAGCATAA GACCGCTAC GCGCATGCG GCGTACCGT AATGATTCAG GTACCGCTGA TTMAAAGA
34801	TATTCGATT CTGCTGATG CCGTACGCG CCGACTGCGA TTTTTTGC CAGTGCAT CAGTGCAT
34901	TCATATGTA AGACTCGGTA AACACATCAG GTTGATTCAG ATCGTCACT GGTAAAGC GACCGAATA
	AGATTACAT TCTGAGGCTT TTGTGTAAT CAACTAATG TAGCGATCA GGTATTTTCT GTGCTTAT
35001	AGACACAT ACAGCCCCA TAGAGGTAT AAGAAATTA TATGCTCTCT TTTTCTGAT TTTTCTGAT
	TCTGTTTAA TGTGCGGCT ATCTTCCATA TGTGTTTAT TGTGTTTAT TGTGTTTAT TGTGTTTAT
35101	TCCGCTTCA GACGCTTCC CAGCGCTCC CAGCGCTCC CAGCGCTCC CAGCGCTCC CAGCGCTCC
	AGGCGAGGT GTTGTGTTAT GTTGTGTTAT GTTGTGTTAT GTTGTGTTAT GTTGTGTTAT GTTGTGTTAT
	GCGACGCT CAATGCTCA CAGTGTAA CAGTGTAA CAGTGTAA CAGTGTAA CAGTGTAA
35201	CCGTGTGTA GTTGTGCTA GTTGTGCTA GTTGTGCTA GTTGTGCTA GTTGTGCTA GTTGTGCTA
	CCAGAGAAC CCGACCGAA CCTACGCCA GAAAGGAG CCAAGAGC CCAAGAGC CCAAGAGC
	GGTCTCTTT GGTGCGCTT GGTGCGCTT GGTGCGCTT GGTGCGCTT GGTGCGCTT GGTGCGCTT

Figure 15V

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35301 CATTTTAAAGAA AACTACAAAT TCCCAACACA TACAGATTAC TCCCTCTTAA AACCTACATC ACCCGCCCTC TTCCCAACCC CCGCGCCACG TCACAAACTC
GTAAATATCT TTTCATGTTA AGGTTGTCT ATGTTCAATG AAGCTGATTT TTGATGCG TGAGCGGCGC AAGCGTGCGG GCGCGGCTGC AGTGTTTGAG

35401 CACCCCTCTA TTATCATATT GCTTCAATC CAAATAAAG TATATTATTG ATATCTTAA TTAAATATTC GATCTGCGA CCGTAAGCTG GATGCCCTT
GTGGGGAGT AATAGTATAA CCGAATTTAG GTTTTATTTCC ATATATATAC TACTACATTT AATTCCTTAA CCTAGACCTT GCGCTCCGAC CTACCGGAAAG

35501 CCCATTATGA TTCTTCTGCG TTCCCGCGGC ATCGGATTC CCGGTTTCCA GGCATGCTG TCCAGGCTAG TACATGCTG AGTCCGCTC ATCTACTGCT GTTGTAGTTC
GGTTATATCT AAGAAGAGCG AAGCGCGCGG TACCGCTAGG GCGGAACTG CCGGTACGAC AGTCCGCTC ATCTACTGCT GTTGTAGTTC GTTGTAGTTC

35601 GCGAGGCAAA GCGCAGGAGC GCTTAAAGAG CCGCTTCTG GCGCTTCTC CATAGCTTC CCGGCGAGT GCTGTAGT TTTTATGCTG CCGATCTGCT
CGTCCCTTTT CCGTCTCTG GATTTTCTC GCGCAGGAG CCGCAAAAG GTATCTGAGG CCGGCGAGT GCTGTAGT TTTTATGCTG CCGATCTGCT

35701 GAGGTGCGGA AACCCGAG GACTATAAAG ATACCAAGCG TTTCGCCCTG GAGCTCTCT CATAGCTTC CCGGCGAGT GCTGTAGT TTTTATGCTG CCGATCTGCT
CTCCACCGCT TTGCGCTGTC CTGATATTTT TATGCTCGC AAGGCGGAC CTTCCAGGGA GCGCGGAGT GCTGTAGT TTTTATGCTG CCGATCTGCT

35801 CTGTCCCGCT TTCTCCCTTC GCGAAGCGTG GCGCTTCTC ATAGCTCAGG TATCTGATG GATCTTCTC CATAGCTTC CCGGCGAGT GCTGTAGT TTTTATGCTG CCGATCTGCT
GACAGCGGGA AAGAGGAG CCGTTCGAC CCGCAAAAG TATCTGATG GATCTTCTC CATAGCTTC CCGGCGAGT GCTGTAGT TTTTATGCTG CCGATCTGCT

35901 TCGACGAGC CCGCTTCTG CCGCTTCTC CCGCAAAAG TATCTGATG GATCTTCTC CATAGCTTC CCGGCGAGT GCTGTAGT TTTTATGCTG CCGATCTGCT
ACGTCTCTG GCGGCAAGTC GCGCTGCGA CCGCAAAAG TATCTGATG GATCTTCTC CATAGCTTC CCGGCGAGT GCTGTAGT TTTTATGCTG CCGATCTGCT

36001 CACTGTATAC AGGATTAGCA GAGCGAGTGA TGTAGGCTG ACATCGGCA CCGCTTCTC CATAGCTTC CCGGCGAGT GCTGTAGT TTTTATGCTG CCGATCTGCT
GTATCCATCT TCTTAATCTG CTGCTCTCAT TGTAGGCTG ACATCGGCA CCGCTTCTC CATAGCTTC CCGGCGAGT GCTGTAGT TTTTATGCTG CCGATCTGCT

36101 ATCTGCTC TCGTGAAGCC AGTTACTTTC GGAANAAGAG TTGTACTC TGTACTGAG TGTACTGAG TGTACTGAG TGTACTGAG TGTACTGAG TGTACTGAG
TAGACGCGAG ACAGCTCTG TCAATGAG CCGTCTCTC GGAANAAGAG TTGTACTC TGTACTGAG TGTACTGAG TGTACTGAG TGTACTGAG TGTACTGAG

36201 AGCAGCAGT TACGCGGAGA AANAAGGAT CTCAAGAGAG TCGTTGATC TTTTCTAGC TTTTCTAGC TTTTCTAGC TTTTCTAGC TTTTCTAGC
TGTCTCTA ATGCGCTCT TTTTCTCTA GATCTCTCT AGTAAATCTAG AANAAGGAT CTCAAGAGAG TCGTTGATC TTTTCTAGC TTTTCTAGC TTTTCTAGC

36301 TTGTGTATG AGATTATCAA AAGGATCTT CACTAGATC CTTTAAATC ATATATATG ATATATATG ATATATATG ATATATATG ATATATATG
AAACGATAC TCTAATAGT TTCTCTAGAA GTGATCTAG GAAATTTAG TTAGATTTCA TATATATCTA TATATATCTA TATATATCTA TATATATCTA

36401 TCAATGAGGC ACCTATCTA GCGTCTCTC TATTTCTCTC ATCCATAGT GCGTCTCTC TATATATCTA TATATATCTA TATATATCTA TATATATCTA TATATATCTA
AGTCACTCG TGTATAGAT CCGTAGACAG ATAAAGCAG TAGGTATCAA CCGCTCTC TATATATCTA TATATATCTA TATATATCTA TATATATCTA TATATATCTA

36501 TGGCGCGAGT GCTGCANTGA TACCGCGAGA CCGCTCTC GCGCTCTC GCGCTCTC TATATATCTA TATATATCTA TATATATCTA TATATATCTA TATATATCTA
ACCGCGTCA CCGCTCTC ATCGCTCTC GCGCTCTC GCGCTCTC TATATATCTA TATATATCTA TATATATCTA TATATATCTA TATATATCTA

36601 CCGTCACTT TATCCCTCTC CATCCAGTCT ATTAATGTTT GCGCGAGT GCGCTCTC TATATATCTA TATATATCTA TATATATCTA TATATATCTA TATATATCTA
GAGCTTGA ATAGCGGAG GTAGCTCAGA TAAATACAA CCGCTCTC TATATATCTA TATATATCTA TATATATCTA TATATATCTA TATATATCTA

36701 CTACAGCAT CCGTCTCTC CCGCTCTC TGTATGCT TTCACTGAG TCGCTCTC TCGCTCTC TCGCTCTC TCGCTCTC TCGCTCTC TCGCTCTC
GATGTCTCTA GCGACAGAT GCGAGCAGTA AACTATAGC AAGTATAGC AAGCGGAG TCGCTCTC TCGCTCTC TCGCTCTC TCGCTCTC TCGCTCTC

36801 AANAAGGAT AGCTCTCTC GCTCTCTCT CCGTCTCTC AGTAAATCTAG AANAAGGAT CCGCTCTC TATATATCTA TATATATCTA TATATATCTA TATATATCTA
TTTCTCTCA TCGAGGAGT CAGGAGCTA GCAATCTCT TCAATCAAC GCGCTCTC TATATATCTA TATATATCTA TATATATCTA TATATATCTA TATATATCTA

36901 GTCATGCGT CCGTAAATG CTTTCTCTG ACCTGAGT ACTTACCAA GTATCTCTA GATATGTTA TGTGCGGAC GATTTCTCT TGTGCGGCT
CACTACGTA GCGATCTCT TACAGAGC TATACACT TATATGCT ACTTACACT ACCTGCGT GCTTACAGT ACCTGCGT

Figure 15W

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37001 CACACGGA TATACCGG CCACATAGA GACTTTAA AGTCTCATC ATTGAAAC GTCTTGGG GCGAAACTC TCAGGATCT TACTTCTCTT
GTGTGCGCT ATTATGCGC GGTGTATGT CTTCGAATTT TACGAGTAG TAACCTTTG CAGGAGGCC CCGTTTGAG AGTTCCTAGA ATGCGGACAA
37101 GAGATCCAGT TCGATGTAC ACCGATTTA TCTTAAAT TTTTAACTT CACTTCTCTT TCTGCTGAG CAAAAACAGG AAGCCAAAT
CTCTAGGTC AACTTACATG GATGACAGG TCGGTGACT AGATTTTAA GAAATGAA GTTCTCTT CAGCCACTC GTTTTCTCC TCCCTTTTAA
37201 GCGGAAAG AGGATTAAG GCGGACAGG AATGTTAA TACTTACTT TTTCTTTT CAAATTTAT GAGCATTAA TCAGCTTAT TCTCTCATCA
CGGCTTTT TCCCTTATC CCGCTTGGC TTACAACTT ATGCTTATTA GAGGAAAG GTTATATTA CTTCOTAAAT AGTCCCAATA ACAGAGTACT
37301 GCGGATACAT ATTGATGT ATTAGAAG ATAAAGAT AGGCTTCTC CCGGATTC CCGGAAAT GCGACCTGAC GTCTAAGAAA CCATTATTAA
CGCTATGTA TAACTTACA TAACTCTT TATTGTTA TCCGCAAGC GCGGTAAAG GCGCTTTCA CCGTGGACTG CAGATCTCTT GGTAAATATA

EcHII
BamHI

37401 CATGACATTA ACCTATAAA ATAGGCTAT CAGGAGGCC TTCTGCTTC AAGATTTGA TCTGATCTT TAAT (SEQ ID NO: 27)
GTACTGTAAAT TGGATATTTT TATCCGATA GTGCTCGTG AAGCGAAG TTCTTAACT AGCTTAAGA ATTA (SEQ ID NO: 28)

Figure 15X

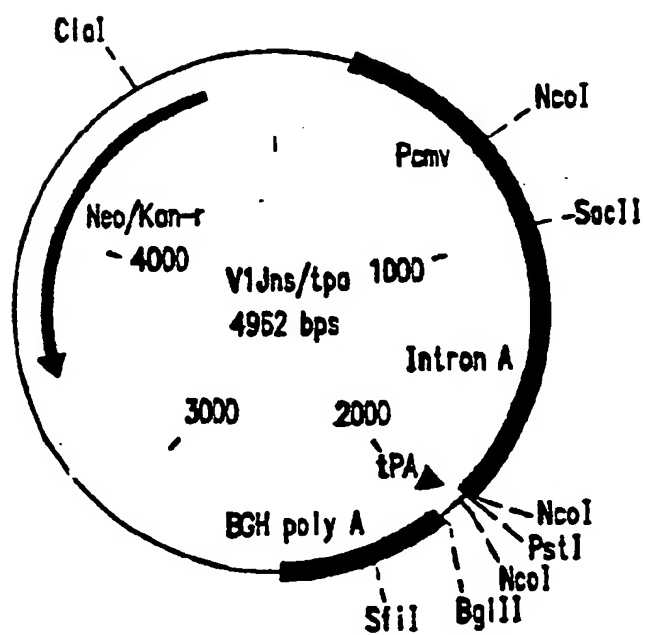
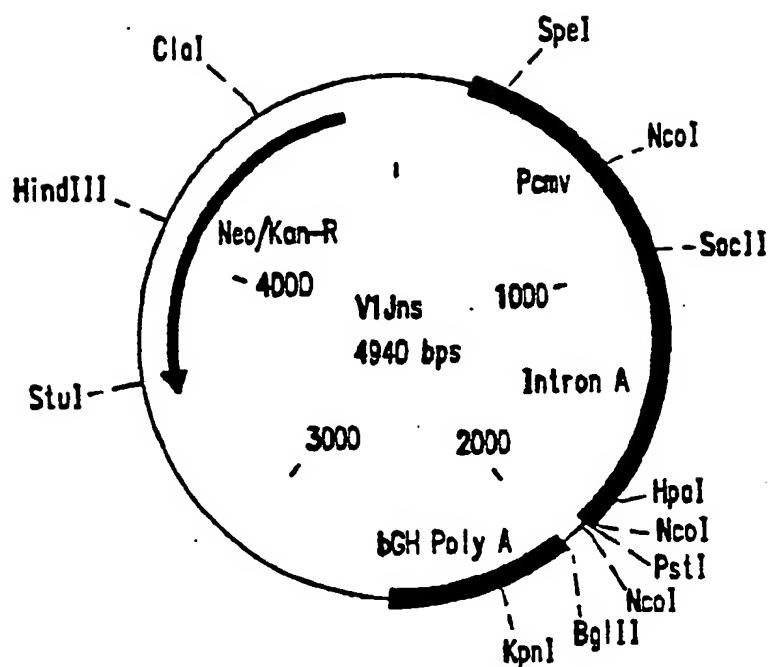


FIGURE 16

AGATCTACCATGGCCCCCATCTCCCCATTGAGACTGTGCCTGTGAAGCTGAAGCCTGGCATGGATGGCCCCAAGGTGAA
 BgIII MetAlaProIleSerProIleGluThrValProValLysLeuLysProGlyMetAspGlyProLysValLys
 1 10 20

GCAGTGGCCCCTGACTGAGGAGAAGATCAAGGCCCTGGTGGAAATCTGCACTGAGATGGAGAAGGAGGGCAAAATCTCCA
 sGlnTrpProLeuThrGluGluLysIleLysAlaLeuValGluIleCysThrGluMetGluLysGluGlyLysIleSerL
 30 40 50

AGATTGGCCCCGAGAACCCCTACAACACCCCTGTGTTTGCCATCAAGAAGAAGGACTCCACCAAGTGGAGGAAGCTGGTG
 ysIleGlyProGluAsnProTyrAsnThrProValPheAlaIleLysLysLysAspSerThrLysTrpArgLysLeuVal
 60 70

GACTTCAGGGAGCTGAACAAGAGGACCCAGGACTTCTGGGAGGTGCAGCTGGGCATCCCCACCCCGCTGGCCTGAAGAA
 AspPheArgGluLeuAsnLysArgThrGlnAspPheTrpGluValGlnLeuGlyIleProHisProAlaGlyLeuLysLys
 80 90 100

GAAGAAGTCTGTGACTGTGCTGGCTGTGGGGATGCCACTTCTCTGTGCCCCCTGGATGAGGACTTCAGGAAGTACACTG
 sLysLysSerValThrValLeuAlaValGlyAspAlaTyrPheSerValProLeuAspGluAspPheArgLysTyrThrA
 110 120 130

CCTTCACCATCCCCCTCCATCAACAATGAGACCCCTGGCATCAGGTACCACTACAATGTGCTGCCCCAGGGCTGSAAGGGC
 loPheThrIleProSerIleAsnAsnGluThrProGlyIleArgTyrGlnTyrAsnValLeuProGlnGlyTrpLysGly
 140 150

TCCCCTGCCATCTTCCAGTCTCCATGACCAAGATCCTGGAGCCCTTCAGGAAGCAGAACCCTGACATTGTGATCTACCA
 SerProAlaIlePheGlnSerSerMetThrLysIleLeuGluProPheArgLysGlnAsnProAspIleValIleTyrGln
 160 170 180

GTACATGGCTGCCCTGTATGTGGCTCTGACCTGGAGATTGGGCAGCACAGGACCAAGATTGAGGAGCTGAGGCAGCACC
 nTyrMetAlaAlaLeuTyrValGlySerAspLeuGluIleGlyGlnHisArgThrLysIleGluGluLeuArgGlnHisL
 190 200 210

TGCTGAGGTGGGGCTGACCACCCCTGACAAGAAGCACCAGAAGGAGCCCCCTTCCCTGTGGATGGGCTATGAGCTGCAC
 euLeuArgTrpGlyLeuThrThrProAspLysLysHisGlnLysGluProProPheLeuTrpMetGlyTyrGluLeuHis
 220 230

CCCCACAAGTGGACTGTGCAGCCCATTTGCTGCTGAGAGGACTCCTGGACTGTGAATGACATCCAGAAGCTGGTGGG
 ProAspLysTrpThrValGlnProIleValLeuProGluLysAspSerTrpThrValAsnAspIleGlnLysLeuValGln
 240 250 260

CAAGCTGAAGTGGGGCTCCCAAATCTACCTGGCATCAAGGTGAGGCAGCTGTGCAAGCTGCTGAGGGGCACCAAGGGCC
 yLysLeuAsnTrpAlaSerGlnIleTyrProGlyIleLysValArgGlnLeuCysLysLeuLeuArgGlyThrLysAlaL
 270 280 290

FIGURE 17A

TGACTGAGGTGATCCCCCTGACTGAGGAGGCTGAGCTGGAGCTGGCTGAGAACAGGCAGATCCTGAAGGAGCCTGTGCAT
 EüThrGluVolIleProLeuThrGluGluAlaGluLeuGluLeuAlaGluAsnArgGluIleLeuLysGluProVolHis
 300 310

GGGGTGACTATGACCCCTCCAAGGACCTGATTGCTGAGATCCAGAAGCAGGGCCAGGGCCAGTGGACCTACCAAAATCTA
 GlyVolTyrTyrAspProSerLysAspLeuIleAlaGluIleGlnLysGlnGlyGlnGlyGlnTrpThrTyrGlnIleTy
 320 330 340

CCAGGAGCCCTTCAAGAACCTGAAGACTGGCAAGTATGCCAGGATGAGGGGGGCCACACCAATGATGTGAAGCAGCTGA
 rGlnGluProPheLysAsnLeuLysThrGlyLysTyrAlaArgMetArgGlyAlaHisThrAsnAspVolLysGlnLeuT
 350 360 370

CTGAGGCTGTGCAGAAGATCACCAGTACTCCATTGTGATCTGGGGCAAGACCCCCAAGTTCAAGCTGCCATCCAGAAG
 hrGluAlaVolGlnLysIleThrThrGluSerIleVolIleTrpGlyLysThrProLysPheLysLeuProIleGlnLys
 380 390

GAGACCTGGGAGACCTGGTGGACTGAGTACTGGCAGGCCACCTGGATCCCTGAGTGGGAGTTTGTAACACCCCCCCCCT
 GluThrTrpGluThrTrpTrpThrGluTyrTrpGlnAlaThrTrpIleProGluTrpGluPheVolAsnThrProProLe
 400 410 420

GGTGAAGCTGTGGTACCAGCTGGAGAAGGAGCCCATTTGTTGGGGCTGAGACCTTCTATGTGGCTGGGGCTGCCAACAGGG
 uVolLysLeuTrpTyrGlnLeuGluLysGluProIleVolGlyAlaGluThrPheTyrVolAlaGlyAlaAlaAsnArgG
 430 440 450

AGACCAAGCTGGGCAAGGCTGGCTATGTGACCAACAGGGGCAGGCAGAAAGTGGTGACCTGACTGACACCACCAACCAG
 luThrLysLeuGlyLysAlaGlyTyrVolThrAsnArgGlyArgGlnLysVolVolThrLeuThrAspThrThrAsnGln
 460 470

AAGACTGCCCTCCAGGCCATCTACCTGGCCCTCCAGGACTCTGGCCTGGAGGTGAACATTGTGACTGCCTCCAGTATGC
 LysThrAlaLeuGlnAlaIleTyrLeuAlaLeuGlnAspSerGlyLeuGluVolAsnIleVolThrAlaSerGlnTyrAl
 480 490 500

CCTGGGCATCATCCAGGCCCAGCCTGATCAGTCTGAGTCTGAGCTGGTGAACCAGATCATTGAGCAGCTGATCAAGAAGG
 aLeuGlyIleIleGlnAlaGlnProAspGlnSerGluSerGluLeuVolAsnGlnIleIleGluGlnLeuIleLysLysG
 510 520 530

AGAAGGTGTACCTGGCCTGGTGCCTGCCACAAGGCCATTGGGGGCAATGAGCAGGTGGACAAGCTGGTGTCTGCTGGC
 luLysVolTyrLeuAlaTrpVolProAlaHisLysGlyIleGlyGlyAsnGluGlnVolAspLysLeuVolSerAlaGly
 540 550

ATCAGGAAGGTGCTGTTCTGGATGGCATTGACAAGGCCAGGATGAGCATGAGAAGTACCACTCCAAGTGGAGGGCTAT
 IleArgLysValLeuPheLeuAspGlyIleAspLysAlaGlnAspGluHisGluLysTyrHisSerAsnTrpArgAlaMe
 560 570 580

FIGURE 17B

GGCCTCTGACTTCAACCTGCCCCCTGTGGTGGCTAAGGAGATTGTGGCTCCCTGTGACAAGTCCAGCTGAAGGGGGAGG
tAlaSerAspPheAsnLeuProProVolVolAlaLysGluIleVolAlaSerCysAspLysCysGlnLeuLysGlyGluA
590 600 610

CCATGCATGGGCAGGTGGACTGCTCCCTGCCATCTGGCAGCTGGCTGCACCCACCTGGAGGGCAAGGTGATCCTGGTG
lAlaMetHisGlyGlnVolAspCysSerProGlyIleTrpGlnLeuAlaCysThrHisLeuGluGlyLysVolIleLeuVol
620 630

GCTGTGCATGTGGCTCCGGCTACATTGAGGCTGAGGTGATCCCTGCTGAGACAGGCCAGGAGACTGCCTACTTCCTGCT
AlaVolHisVolAlaSerGlyTyrIleGluAlaGluVolIleProAlaGluThrGlyGlnGluThrAlaTyrPheLeuLe
640 650 660

GAAGCTGGCTGGCAGGTGGCTGTGAAGACCATCCACACTGCCAATGGCTCCAACCTTCACTGGGGCCACAGTGAGGGCTG
uLysLeuAlaGlyArgTrpProVolLysThrIleHisThrAlaAsnGlySerAsnPheThrGlyAlaThrVolArgAlaA
670 680 690

CCTGCTGGTGGCTGGCATCAAGCAGGAGTTTGGCATCCCTACAACCCCCAGTCCCAGGGGGTGGTGGCTCCATGAAC
lAlaCysTrpTrpAlaGlyIleLysGlnGluPheGlyIleProTyrAsnProGlnSerGlnGlyVolVolAlaSerMetAsn
700 710

AAGGAGCTGAAGAAGATCATTGGGCAGGTGAGGGACCAGGCTGAGCACCTGAAGACAGCTGTGCAGATGGCTGTGTTTCA
LysGluLeuLysLysIleIleGlyGlnVolArgAspGlnAlaGluHisLeuLysThrAlaVolGlnMetAlaVolPheIle
720 730 740

CCACAACCTTCAAGAGGAAGGGGGCATCGGGGGCTACTCCGCTGGGGAGAGGATTGTGGACATCATTGCCACAGACATCC
eHisAsnPheLysArgLysGlyGlyIleGlyGlyTyrSerAlaGlyGluArgIleVolAspIleIleAlaThrAspIleG
750 760 770

AGACCAAGGAGCTCCAGAAGCAGATCACCAAGATCCAGAACTTCAGGTGTACTACAGGACTCCAGGAACCCCTGTGG
InThrLysGluLeuGlnLysGlnIleThrLysIleGlnAsnPheArgVolTyrTyrArgAspSerArgAsnProLeuTrp
780 790

AAGGGCCCTGCCAAGCTGCTGTGGAAGGGGGAGGGGGCTGTGGTGATCCAGGACAACCTCTGACATCAAGGTGGTGGCCAG
LysGlyProAlaLysLeuLeuTrpLysGlyGluGlyAlaVolVolIleGlnAspAsnSerAspIleLysVolVolProAr
800 810 820

GAGGAAGGCCAAGATCATCAGGGACTATGGCAAGCAGATGGCTGGGGATGACTGTGTGGCTCCAGGCAGGATGAGGACT
gArgLysAlaLysIleIleArgAspTyrGlyLysGlnMetAlaGlyAspAspCysVolAlaSerArgGlnAspGluAspx
830 840 850

AAAGCCCGGGCAGATCT (SEQ ID NO: 3)
Xx BgII (SEQ ID NO: 4)

FIGURE 17C

GATCACCATGCATGCAATGAAGACAGAGCCCTCGCTGCTGCTGCCGTGGTGGACCACTTCGTTCCG
MetAspAlaMetLysArgGlyLeuCysCysValLeuleuleucCysGlyAlaValPheValSerP
-25 -20 -10

CCAGCGAGATCTCGCGCCCCCATCTGCCCATTGAGACTGTGCCGTGAAGCTGAGCCCTGCCATGCATGCC
RoSerGluIleSerAlaProIleSerProIleGluThrValProValLysLeuYsProGlyMetAspGly
-1 2 10 20

FIGURE 18

WT	- ATG GGT GGC AAG TGG TCA AAA CGT AGT GTG CCT GGA TGG TCT	-42
OPT	- ATG GGC GGC AAG TGG TCC AAG AGG TCC GTG CCC GGC TGG TCC M G G K W S K R S V P G W S	-14
WT	- ACT GTA AGG GAA AGA ATG AGA CGA GCT GAG CCA GCA GCA GAT	-84
OPT	- ACC GTG AGG GAG AGG ATG AGG AGG GCC GAG CCC GCC GCC GAC T V R E R H R R A E P A A D	-28
WT	- AGG GTG AGA CGA ACT GAG CCA GCA GCA GTA GGG GTG GGA GCA	-126
OPT	- AGG GTG AGG AGG ACC GAG CCC GCC GCC GTG GGC GTG GGC GCC R V R R T E P A A V G V G A	-42
WT	- GTA TCT CGA GAC CTG GAA AAA CAT GGA GCA ATC ACA AGT AGC	-168
OPT	- GTG TCC AGG GAC CTG GAG AAG CAC GGC GCC ATC ACC TCC TCC V S R D L E K H G A I T S S	-56
WT	- AAT ACA GCA GCT ACC AAT GCT GAT TGT GCC TGG CTA GAA GCA	-210
OPT	- AAC ACC GCC GCC ACC AAC GCC GAC TGC GCC TGG CTG GAG GCC N T A A T N A D C A W L E A	-70
WT	- CAA GAG GAT GAG GAA GTG GGT TTT CCA GTC AGA CCT CAG GTA	-252
OPT	- CAG GAG GAC GAG GAG GTG GGC TTC CCC GTG AGG CCC CAG GTG Q E D E E V G F P V R P Q V	-84
WT	- CCT TTA AGA CCA ATG ACT TAC AAG GGA GCT GTA GAT CTT AGC	-294
OPT	- CCC CTG AGG CCC ATG ACC TAC AAG GGC GCC GTG GAC CTG TCC P L R P M T Y K G A V D L S	-98
WT	- CAC TTT TTA AAA GAA AAG GGG GGA CTG GAA GGG CTA ATT CAC	-336
OPT	- CAC TTC CTG AAG GAG AAG GGC GGC CTG GAG GGC CTG ATC CAC H F L K E K G G L E G L I H	-112
WT	- TCA CAG AAA AGA CAA GAT ATC CTT GAT CTG TGG GTC TAC CAC	-378
OPT	- TCC CAG AAG AGG CAG GAC ATC CTG GAC CTG TGG GTG TAC CAC S Q K R Q D I L D L W V Y H	-126
WT	- ACA CAA GGC TAC TTC CCT GAT TGG CAG AAC TAC ACA CCA GGG	-420
OPT	- ACC CAG GGC TAC TTC CCC GAC TGG CAG AAC TAC ACC CCC GGC T Q G Y F P D W D N Y T P G	-140

FIGURE 19A

WT	- CCA GGA ATC AGA TTT CCA TTG ACC TTT GGA TGG TGC TTC AAG	-462
OPT	- CCC GGC ATC AGG TTC CCC CTG ACC TTC GGC TGG TGC TTC AAG	
	P G I R F P L T F G W C F K	-154
WT	- CTA GTA CCA GTT GAG CCA GAA AAG GTA GAA GAG GCC AAT GAA	-504
OPT	- CTG GTG CCC GTG GAG CCC GAG AAG GTG GAG GAG GCC AAC GAG	
	L V P V E P E K V E E A N E	-168
WT	- GGA GAG AAC AAC TGC TTG TTA CAC CCT ATG AGC CAG CAT GGG	-546
OPT	- GGC GAG AAC AAC TGC CTG CTG CAC CCC ATG TCC CAG CAC GGC	
	G E N N C L L H P M S Q H G	-182
WT	- ATA GAG GAC CCG GAG AAG GAA GTG TTA GAG TGG AGG TTT GAC	-588
OPT	- ATC GAG GAC CCC GAG AAG GAG GTG CTG GAG TGG AGG TTC GAC	
	I E D P E K E V L E W R F D	-196
WT	- AGC AAG CTA GCA TTT CAT CAC GTG GCC CGA GAG CTG CAT CCG	-630
OPT	- TCC AAG CTG GCC TTC CAC CAC GTG GCC AGG GAG CTG CAC CCC	
	S K L A F H H V A R E L H P	-210
WT	- GAG TAC TAC AAG GAC TGC TGA (SEQ ID NO:30)	-651
OPT	- GAG TAC TAC AAG GAC TGC TAA (contained within SEQ ID NO:9)	
	E Y Y K D C (SEQ ID NO:10)	-216

FIGURE 19B

V1Jns/nef *PstI* *BglII*
 CATGGGTCCTTTTCTGGAGTCACCGTCTTGGAGATCTGACC ACC ATG GGC GGC ANG TGG TCC ANG AGG TCC GTG CCC
 M G G K W S K R S V P

. CAC CCC GAG TAC TAC ANG GAC TGC TAA *SrfI* *BglII*
 H P E Y Y K D C * AGCCCGGGCAGATCTGCTGTGCGCTTCTAGTTGCCAGC (SEQ ID NO: 38)
 (contained within SEQ ID NO: 10)

V1Jns/nef(G2A.LLAA)

PstI *BglII*
 CATGGGTCCTTTTCTGGAGTCACCGTCTTGGAGATCTGACC ACC ATG GGC GGC ANG TGG TCC ANG AGG TCC GTG CCC
 M A G K W S K R S V P

. CAC CCC GAG TAC TAC ANG GAC TGC TAA *SrfI* *BglII*
 H P E Y Y K D C * AGCCCGGGCAGATCTGCTGTGCGCTTCTAGTTGCCAGC (SEQ ID NO: 39)
 (contained within SEQ ID NO: 14)

V1Jns/tpanef & V1Jns/tpanef(LLAA)

PstI *BglII*
 CATGGGTCCTTTTCTGGAGTCACCGTCTTATATCTAGATCACC ATG GAT GCA ATG AGA GGG CTC TGC TGT GTG
 M D A M K R G L C C V

CTG CTG CTG TGT GGA GCA GTC TTC GTT TCG CCC AGC GAG ATC TCC TCC ANG AGG TCC GTG CCC
 L L L C G A V F V S P S E I S S K R S V P

. CAC CCC GAG TAC TAC ANG GAC TGC TAA *SrfI* *BglII*
 H P E Y Y K D C * AGCCCGGGCAGATCTGCTGTGCGCTTCTAGTTGCCAGC (SEQ ID NO: 40)
 (contained within SEQ ID NO: 16)

FIGURE 20

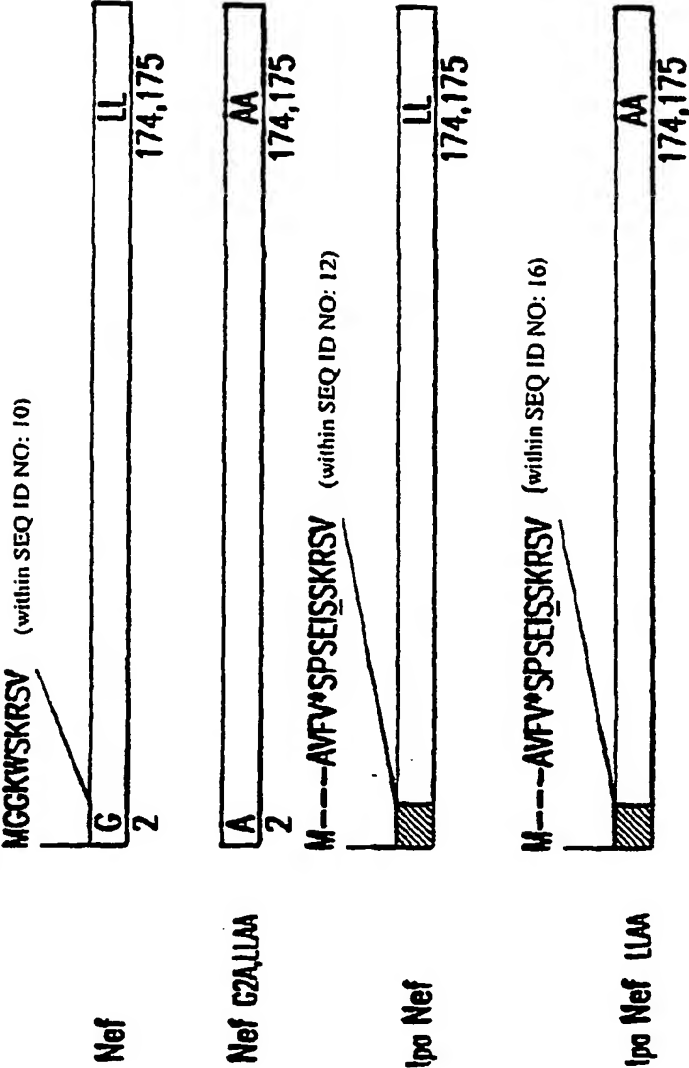


FIGURE 21

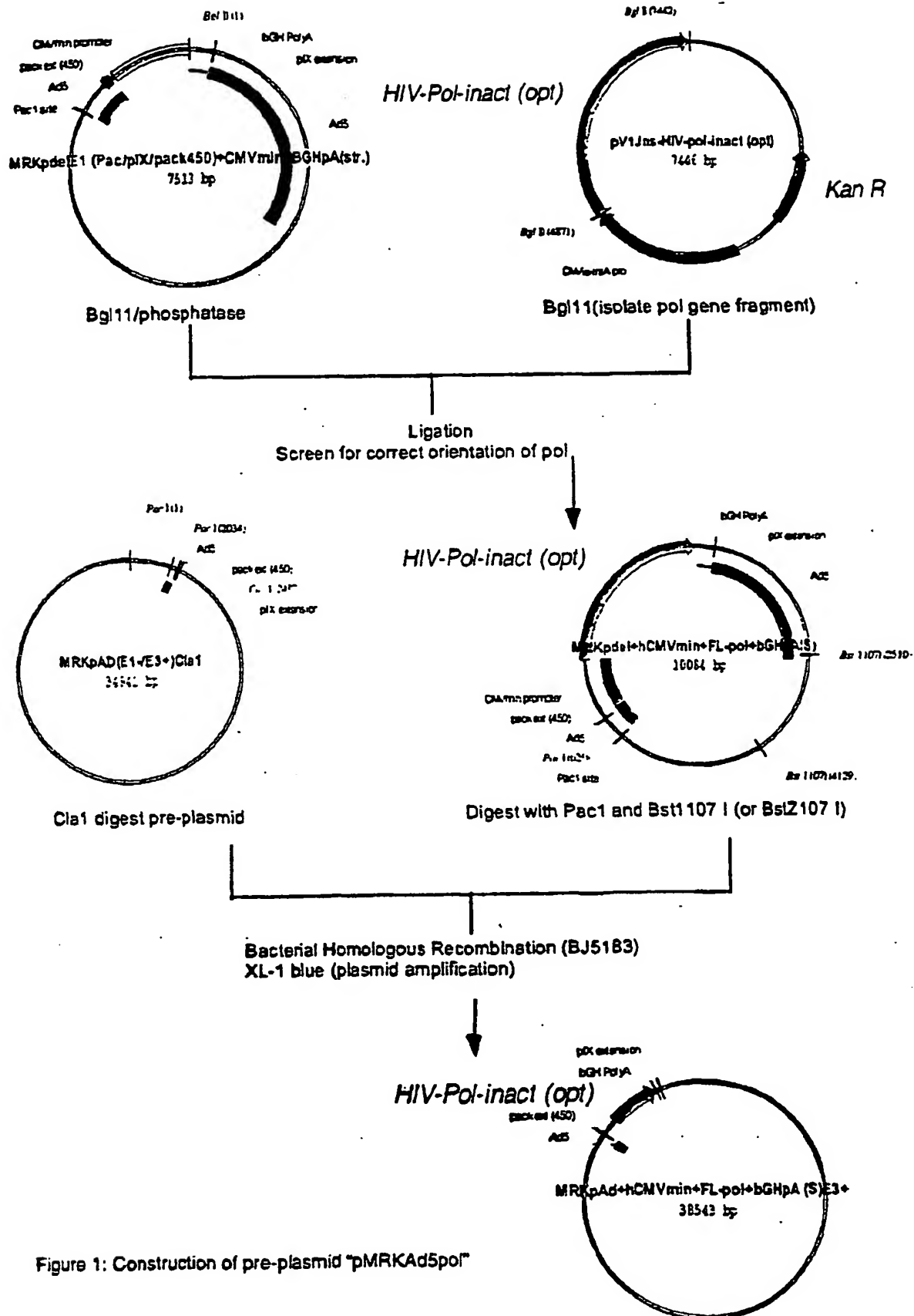


Figure 1: Construction of pre-plasmid "pMRKAd5pol"

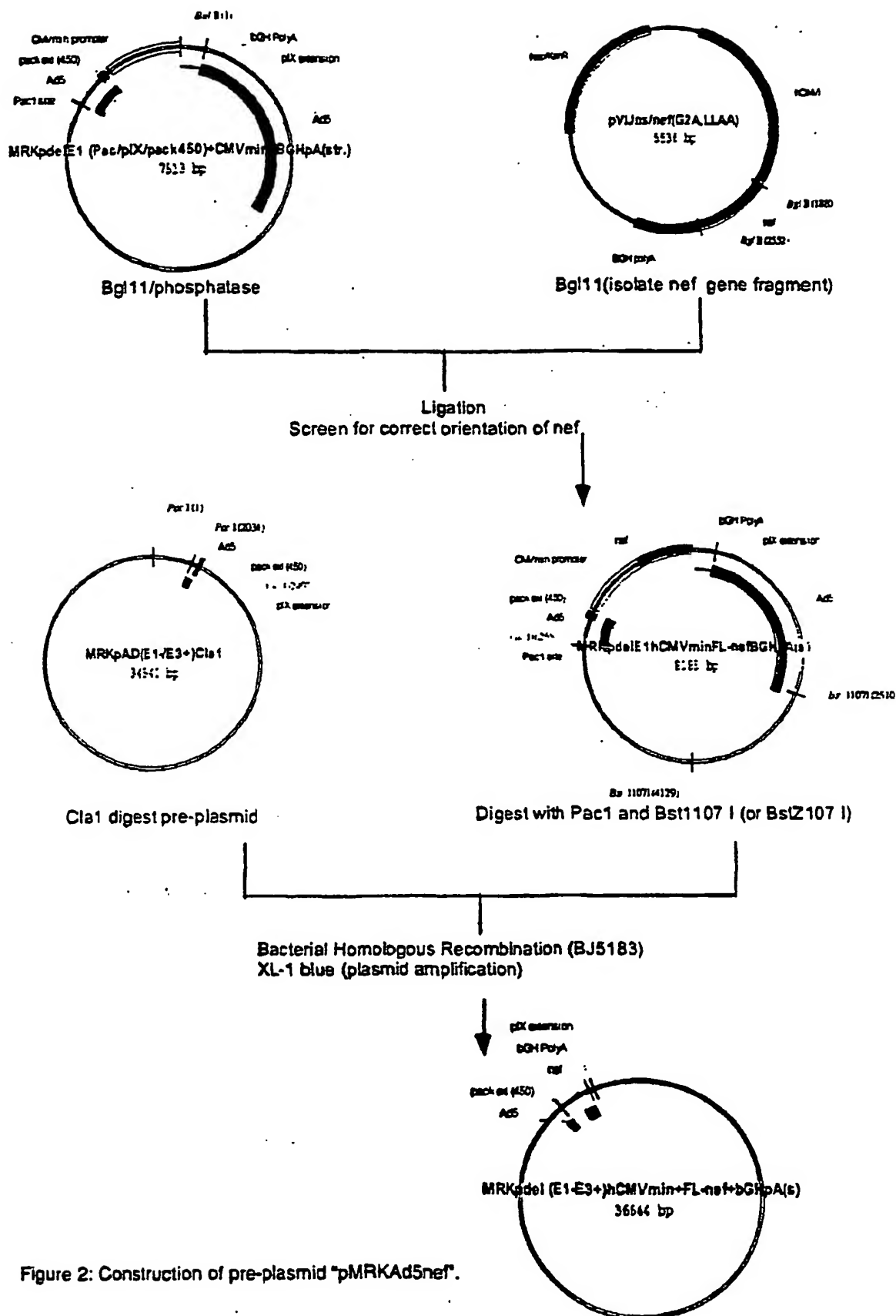
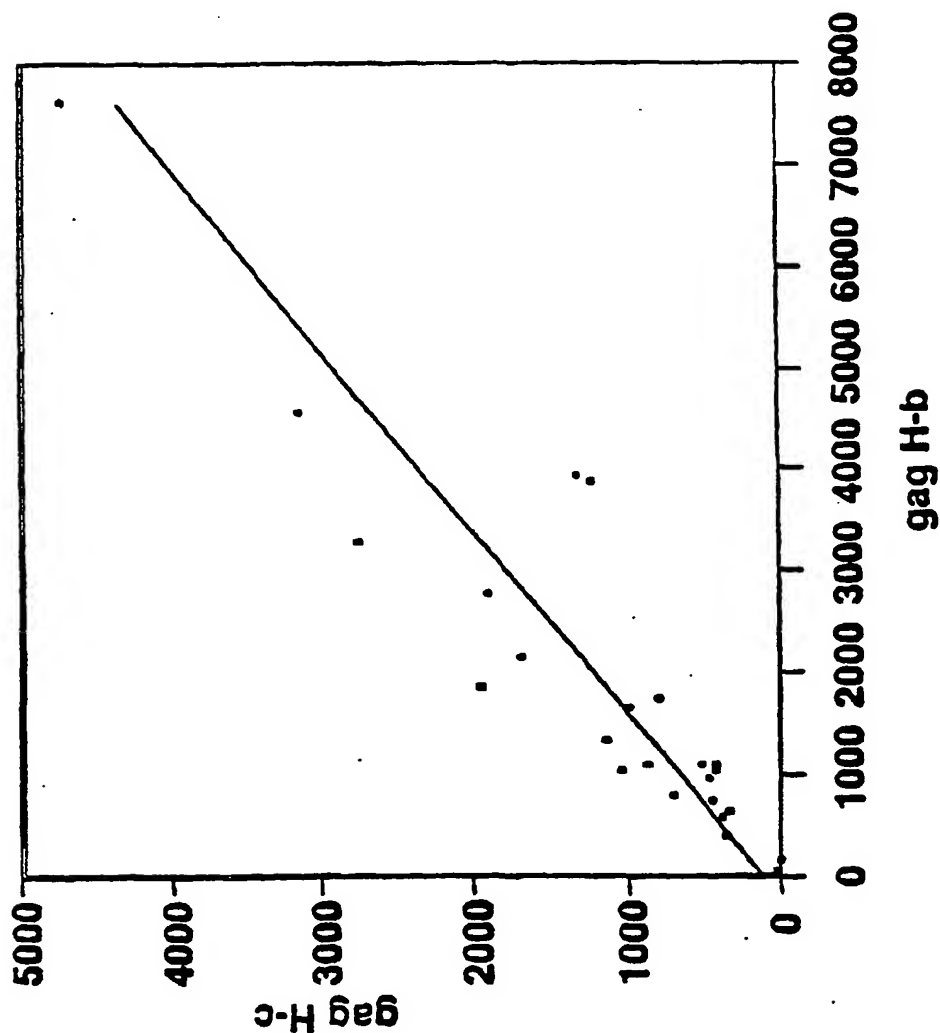


Figure 2: Construction of pre-plasmid "pMRKAd5nef".

Comparison of Clade B vs. Clade C Anti-gag T Cell Responses in Clade B HIV-Infected Subjects



Comparison of Clade B vs. Clade C Anti-nef T Cell Responses in Clade B HIV-Infected Subjects

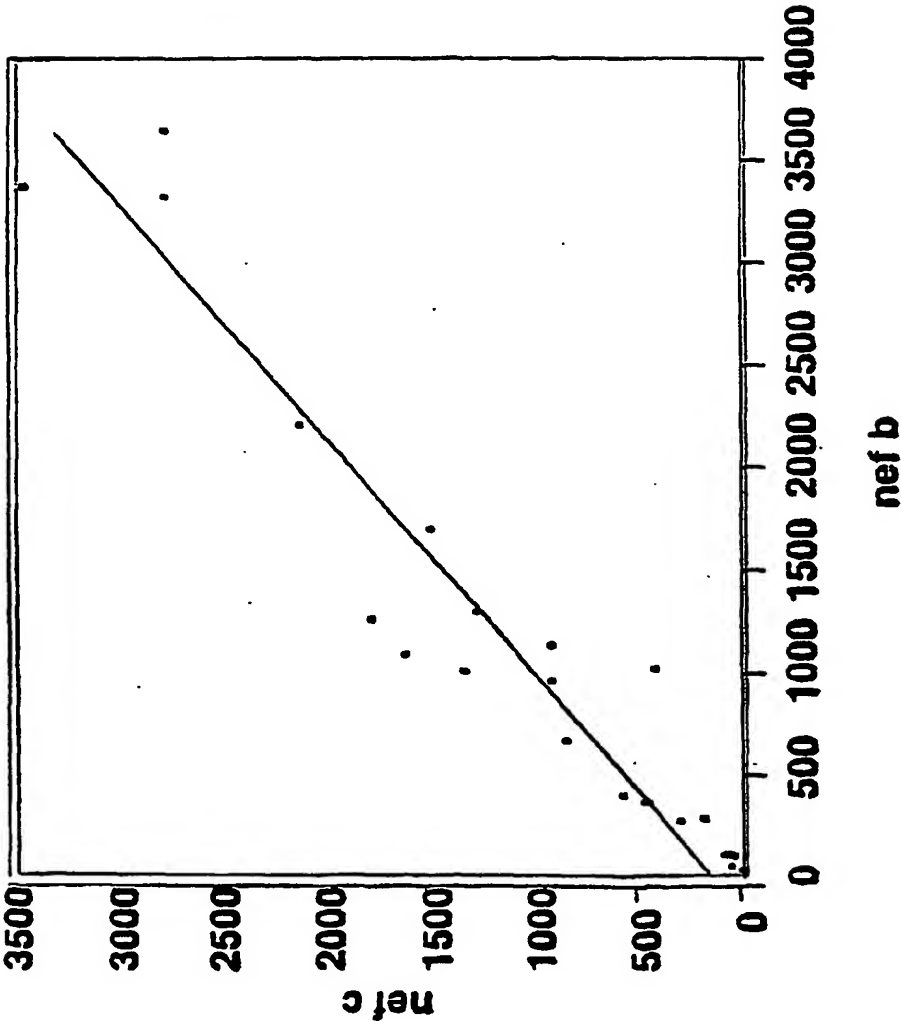


FIGURE 25

MRKAd5pol MER1062
(MRKAd5 Pre-Adenoviral Vector Containing the IA opt pol Coding Region)

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1  CATCATCAAT AATATACCTT ATTTTGGATT GAAGCCAATA TGATAATGAG
   GTAGTAGTTA TTATATGGAA TAAACCTAA CTCGGTTAT ACTATTACTC

51  GGGGTGGAGT TTGTGACGTG GCGCGGGGCG TGGGAACGGG GCGGGTGACG
   CCCACCTCA AACACTGCAC CGCGCCCCGC ACCCTTGCCC CGCCCACTGC

101 TAGTAGTGTG GCGGAAGTGT GATGTTGCAA GTGTGGCGGA ACACATGTAA
   ATCATCACAC CGCCTTCACA CTACAACGTT CACACCGCCT TGTGTACATT

151 GCGACGGATG TGGCAAAAGT GACGTTTTTG GTGTGCGCCG GTGTACACAG
   CGCTGCCTAC ACCGTTTTCA CTGCAAAAAC CACACGCGGC CACATGTGTC

201 GAAGTGACAA TTTTCGCGCG GTTTTAGGCG GATGTTGTAG TAAATTTGGG
   CTTCACTGTT AAAAGCGCGC CAAATCCGC CTACAACATC ATTTAAACCC

251 CGTAACCGAG TAAGATTTGG CCATTTTCGC GGGAAACTG AATAAGAGGA
   GCATTGGCTC ATTCTAAACC GGTAAAAGCG CCCTTTTGAC TTATTCTCCT

301 AGTGAAATCT GAATAATTTT GTGTTACTCA TAGCGCGTAA TATTTGTCTA
   TCACTTTAGA CTTATTAAAA CACAATGAGT ATCGCGCATT ATAAACAGAT

351 GGGCCGCGGG GACTTTGACC GTTTACGTGG AGACTCGCCC AGGTGTTTTT
   CCCGGCGCCC CTGAAACTGG CAAATGCACC TCTGAGCGGG TCCACAAAA

401 CTCAGGTGTT TTCCGCGTTC CGGGTCAAAG TTGGCGTTTT ATTATTATAG
   GAGTCCACAA AAGGCGCAAG GCCCAGTTTC AACCACAAA TAATAATATC

451 GCGGCCGCGA TCCATTGCAT ACGTTGTATC CATATCATAA TATGTACATT
   CGCCGGCGCT AGGTAACGTA TGCAACATAG GTATAGTATT ATACATGTAA

501 TATATTGGCT CATGTCCAAC ATTACCGCCA TGTTGACATT GATTATTGAC
   ATATAACCGA GTACAGGTG TAATGGCGGT ACAACTGTAA CTAATAACTG

551 TAGTTATTAA TAGTAATCAA TTACGGGGTC ATTAGTTCAT AGCCCATATA
   ATCAATAATT ATCATTAGTT AATGCCCCAG TAATCAAGTA TCGGGTATAT

601 TGGAGTTCCG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG
   ACCTCAAGGC GCAATGTATT GAATGCCATT TACCGGGCGG ACCGACTGGC

651 CCCAACGACC CCCGCCCAT TACGTCAATA ATGACGTATG TTCCCATAGT
   GGGTTGCTGG GGGCGGGTAA CTGCAGTTAT TACTGCATAC AAGGGTATCA

701 AACGCCAATA GGGACTTTCC ATTGACGTCA ATGGGTGGAG TATTTACGGT
   TTGCGGTTAT CCCTGAAAGG TAACTGCAGT TACCCACCTC ATAAATGCCA

751 AACTGCCCA CTTGGCAGTA CATCAAGTGT ATCATATGCC AAGTACGCCC
   TTTGACGGGT GAACCGTCAT GTAGTTCACA TAGTATACGG TTCATGCGGG

801 CCTATTGACG TCAATGACGG TAAATGGCCC GCCTGGCATT ATGCCAGTA
   GGATAACTGC AGTTACTGCC ATTTACGGG CGGACCGTAA TACGGGTGTCAT

851 CATGACCTTA TGGGACTTTC CTACTTGGCA GTACATCTAC GTATTAGTCA
   GTACTGGAAT ACCCTGAAAG GATGAACCGT CATGTAGATG CATAATCAGT

```

Figure 26A

901 TCGCTATTAC CATGGTGATG CGGTTTGGC AGTACATCAA TGGGCGTGGA
AGCGATAATG GTACCACTAC GCCAAAACCG TCATGTAGTT ACCCGCACCT

951 TAGCGGTTTG ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA
ATCGCCAAAC TGAGTGCCCC TAAAGGTTCA GAGGTGGGGT AACTGCAGTT

1001 TGGGAGTTTG TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA
ACCCCTCAAAC AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT

1051 ACAACTCCGC CCCATTGACG CAAATGGGCG GTAGGCGTGT ACGGTGGGAG
TGTTGAGGCG GGGTAACTGC GTTTACCCGC CATCCGCACA TGCCACCCTC

1101 GTCTATATAA GCAGAGCTCG TTTAGTGAAC CGTCAGATCG CCTGGAGACG
CAGATATATT CGTCTCGAGC AAATCACTTG GCAGTCTAGC GGACCTCTGC

1151 CCATCCACGC TGTTTTGACC TCCATAGAAG ACACCGGGAC CGATCCAGCC
GGTAGGTGCG ACAAACCTGG AGGTATCTTC TGTGGCCCTG GCTAGGTGCG

1201 TCCGCGGCCG GGAACGGTGC ATTGGAACGC GGATTCCCCG TGCCAAGAGT
AGGCGCCGGC CCTTGCCACG TAACCTTGCG CCTAAGGGGC ACGGTTCTCA

1251 GAGATCTACC ATGGCCCCCA TCTCCCCCAT TGAGACTGTG CCTGTGAAGC
CTCTAGATGG TACCGGGGGT AGAGGGGGTA ACTCTGACAC GGACACTTCG

1301 TGAAGCCTGG CATGGATGGC CCCAAGGTGA AGCAGTGGCC CCTGACTGAG
ACTTCGGACC GTACCTACCG GGGTTCCACT TCGTCACCGG GGACTGACTC

1351 GAGAAGATCA AGGCCCTGGT GGAAATCTGC ACTGAGATGG AGAAGGAGGG
CTCTTCTAGT TCCGGGACEA CCTTTAGACG TGACTCTACC TCTTCCTCCC

1401 CAAAATCTCC AAGATTGGCC CCGAGAACCC CTACAACACC CCTGTGTTTG
GTTTTAGAGG TTCTAACCGG GGCTCTTGGG GATGTTGTGG GGACACAAAC

1451 CCATCAAGAA GAAGGACTCC ACCAAGTGA GGAAGCTGGT GGACTTCAGG
GGTAGTTCTT CTTCTGAGG TGGTTCACCT CTTTCGACCA CCTGAAGTCC

1501 GAGCTGAACA AGAGGACCCA GGACTTCTGG GAGGTGCAGC TGGGCATCCC
CTCGACTTGT TCTCCTGGGT CCTGAAGACC CTCCACGTCG ACCCGTAGGG

1551 CCACCCCGCT GGCCTGAAGA AGAAGAAGTC TGTGACTGTG CTGGCTGTGG
GGTGGGGCGA CCGGACTTCT TCTTCTTCAG AACTGACAC GACCGACACC

1601 GGGATGCCTA CTTCTCTGTG CCCCTGGATG AGGACTTCAG GAAGTACACT
CCCTACGGAT GAAGAGACAC GGGGACCTAC TCCTGAAGTC CTTTCATGTGA

1651 GCCTTCACCA TCCCCTCCAT CAACAATGAG ACCCCTGGCA TCAGGTACCA
CGGAAGTGGT AGGGGAGGTA GTTGTTACTC TGGGGACCGT AGTCCATGGT

1701 GTACAATGTG CTGCCCCAGG GCTGGAAGGG CTCCCCTGCC ATCTTCCAGT
CATGTTACAC GACGGGGTCC CGACCTTCCC GAGGGGACGG TAGAAGGTCA

1751 CCTCCATGAC CAAGATCCTG GAGCCCTTCA GGAAGCAGAA CCCTGACATT
GGAGGTACTG GTTCTAGGAC CTCGGGAAGT CCTTCGTCTT GGGACTGTAA

1801 GTGATCTACC AGTACATGGC TGCCCTGTAT GTGGGCTCTG ACCTGGAGAT
CACTAGATGG TCATGTACCG ACGGGACATA CACCCGAGAC TGGACCTCTA

Figure 24B

1901	GGGGCCTGAC	CACCCCTGAC	AAGAAGCACC	AGAAGGAGCC	CCCCCTCCTG
	CCCCGGACTG	GTGGGGACTG	TTCTTCGTGG	TCTTCCTCGG	GGGGAAGGAC
1951	TGGATGGGCT	ATGAGCTGCA	CCCCGACAAG	TGGACTGTGC	AGCCCATTGT
	ACCTACCCGA	TACTCGACGT	GGGGCTGTTC	ACCTGACACG	TCGGGTAAAC
2001	GCTGCCTGAG	AAGGACTCCT	GGACTGTGAA	TGACATCCAG	AAGCTGGTGG
	CGACGGACTC	TTCCTGAGGA	CCTGACACTT	ACTGTAGGTC	TTCGACCACC
2051	GCAAGCTGAA	CTGGGCCTCC	CAAATCTACC	CTGGCATCAA	GGTGAGGCAG
	CGTTTCGACTT	GACCCGGAGG	GTTTAGATGG	GACCGTAGTT	CCACTCCGTC
2101	CTGTGCAAGC	TGCTGAGGGG	CACCAAGGCC	CTGACTGAGG	TGATCCCCCT
	GACACGTTTCG	ACGACTCCCC	GTGGTTCCGG	GACTGACTCC	ACTAGGGGGA
2151	GACTGAGGAG	GCTGAGCTGG	AGCTGGCTGA	GAACAGGGAG	ATCCTGAAGG
	CTGACTCCTC	CGACTCGACC	TCGACCGACT	CTTGTCCCTC	TAGGACTTCC
2201	AGCCTGTGCA	TGGGGTGTAC	TATGACCCCT	CCAAGGACCT	GATTGCTGAG
	TCGGACACGT	ACCCACATG	ATACTGGGGA	GGTTCCTGGA	CTAACGACTC
2251	ATCCAGAAGC	AGGGCCAGGG	CCAGTGGACC	TACCAAATCT	ACCAGGAGCC
	TAGGTCTTCG	TCCCGGTCCC	GGTCACCTGG	ATGGTTTAGA	TGGTCCCTCG
2301	CTTCAAGAAC	CTGAAGACTG	GCAAGTATGC	CAGGATGAGG	GGGGCCCACA
	GAAGTTCTTG	GACTTCTGAC	CGTTCATACG	GTCCTACTCC	CCCCGGGTGT
2351	CCAATGATGT	GAAGCAGCTG	ACTGAGGCTG	TGCAGAAGAT	CACCACTGAG
	GGTTACTACA	CTTCGTCGAC	TGACTCCGAC	ACGTCTTCTA	GTGGTGACTC
2401	TCCATTGTGA	TCTGGGGCAA	GACCCCCAAG	TTCAAGCTGC	CCATCCAGAA
	AGGTAACACT	AGACCCCGTT	CTGGGGGTTC	AAGTTCGACG	GGTAGGTCTT
2451	GGAGACCTGG	GAGACCTGGT	GGACTGAGTA	CTGGCAGGCC	ACCTGGATCC
	CCTCTGGACC	CTCTGGACCA	CCTGACTCAT	GACCGTCCGG	TGGACCTAGG
2501	CTGAGTGGGA	GTTTGTGAAC	ACCCCCCCCC	TGGTGAAGCT	GTGGTACCAG
	GACTCACCTT	CAAACACTTG	TGGGGGGGGG	ACCACTTCGA	CACCATGGTC
2551	CTGGAGAAGG	AGCCCATTGT	GGGGGCTGAG	ACCTTCTATG	TGGCTGGGGC
	GACCTCTTCC	TCGGGTAACA	CCCCCGACTC	TGGAAGATAC	ACCGACCCCG
2601	TGCCAACAGG	GAGACCAAGC	TGGGCAAGGC	TGGCTATGTG	ACCAACAGGG
	ACGGTTGTCC	CTCTGGTTCG	ACCCGTTCCG	ACCGATACAC	TGGTTGTCCC
2651	GCAGGCAGAA	GGTGGTGACC	CTGACTGACA	CCACCAACCA	GAAGACTGCC
	CGTCCGTCTT	CCACCACTGG	GACTGACTGT	GGTGGTTGGT	CTTCTGACGG
2701	CTCCAGGCCA	TCTACCTGGC	CCTCCAGGAC	TCTGGCCTGG	AGGTGAACAT
	GAGGTCCGGT	AGATGGACCG	GGAGGTCCTG	AGACCGGACC	TCCACTTGTA
2751	TGTGACTGCC	TCCCAGTATG	CCCTGGGCAT	CATCCAGGCC	CAGCCTGATC
	ACACTGACGG	AGGGTCATAC	GGGACCCGTA	GTAGGTCCGG	GTCGGACTAG

Figure 26 C

2851 GAGAAGGTGT ACCTGGCCTG GGTGCCTGCC CACAAGGGCA TTGGGGGCAA
CTCTTCCACA TGGACCGGAC CCACGGACGG GTGTTCCTCGT AACCCCGTT

2901 TGAGCAGGTG GACAAGCTGG TGTCTGCTGG CATCAGGAAG GTGCTGTTCC
ACTCGTCCAC CTGTTCGACC ACAGACGACC GTAGTCCTTC CACGACAAGG

2951 TGGATGGCAT TGACAAGGCC CAGGATGAGC ATGAGAAGTA CCACTCCAAC
ACCTACCGTA ACTGTTCCGG GTCCTACTCG TACTCTTCAT GGTGAGGTTG

3001 TGGAGGGCTA TGGCCTCTGA CTTCAACCTG CCCCCTGTGG TGGCTAAGGA
ACCTCCCGAT ACCGGAGACT GAAGTTGGAC GGGGGACACC ACCGATTCTT

3051 GATTGTGGCC TCCTGTGACA AGTGCCAGCT GAAGGGGGAG GCCATGCATG
CTAACACCGG AGGACACTGT TCACGGTCGA CTCCCCCTC CGGTACGTAC

3101 GGCAGGTGGA CTGCTCCCCT GGCATCTGGC AGCTGGCCTG CACCCACCTG
CCGTCCACCT GACGAGGGGA CCGTAGACCG TCGACCGGAC GTGGGTGGAC

3151 GAGGGCAAGG TGATCCTGGT GGCTGTGCAT GTGGCCTCCG GCTACATTGA
CTCCCGTTCC ACTAGGACCA CCGACACGTA CACCGGAGGC CGATGTAAT

3201 GGCTGAGGTG ATCCCTGCTG AGACAGGCCA GGAGACTGCC TACTTCCTGC
CCGACTCCAC TAGGGACGAC TCTGTCCGGT CCTCTGACGG ATGAAGGACG

3251 TGAAGCTGGC TGGCAGGTGG CCTGTGAAGA CCATCCACAC TGCCAATGGC
ACTTCGACCG ACCGTCCACC GGACACTTCT GGTAGGTGTG ACGGTTACCG

3301 TCCAAC TTCA CTGGGGCCAC AGTGAGGGCT GCCTGCTGGT GGGCTGGCAT
AGGTTGAAGT GACCCCGGTG TCACTCCCGA CGGACGACCA CCCGACCGTA

3351 CAAGCAGGAG TTTGGCATCC CCTACAACCC CCAGTCCCAG GGGGTGGTGG
GTTCTCCTC AAACCGTAGG GGATGTTGGG GGTGAGGGTC CCCCACCACC

3401 CCTCCATGAA CAAGGAGCTG AAGAAGATCA TTGGGCAGGT GAGGGACCAG
GGAGGTACTT GTTCTCGAC TTCTTCTAGT AACCCGTCCA CTCCCTGGTC

3451 GCTGAGCACC TGAAGACAGC TGTGCAGATG GCTGTGTTCA TCCACAAC TT
CGACTCGTGG ACTTCTGTG ACACGTCTAC CGACACAAGT AGGTGTTGAA

3501 CAAGAGGAAG GGGGGCATCG GGGGCTACTC CGCTGGGGAG AGGATTGTGG
GTTCTCCTTC CCCCCGTAGC CCCCAGTAG GCGACCCCTC TCCTAACACC

3551 ACATCATTGC CACAGACATC CAGACCAAGG AGCTCCAGAA GCAGATCACC
TGTAAGTAACG GTGTCTGTAG GTCTGGTTCC TCGAGGTCTT CGTCTAGTGG

3601 AAGATCCAGA ACTTCAGGGT GTACTACAGG GACTCCAGGA ACCCCCTGTG
TTCTAGGTCT TGAAGTCCCA CATGATGTCC CTGAGGTCTT TGGGGGACAC

3651 GAAGGGCCCT GCCAAGCTGC TGTGGAAGGG GGAGGGGGCT GTGGTGATCC
CTTCCCGGGA CGGTTCGACG ACACCTTCCC CCTCCCCCGA CACCACTAGG

3701 AGGACAAC TC TGACATCAAG GTGGTGCCCA GGAGGAAGGC CAAGATCATC
TCCTGTTGAG ACTGTAGTTC CACCACGGGT CCTCCTTCCG GTTCTAGTAG

Figure 26 D

3801 GGATGAGGAC TAAAGCCCGG GCAGATCTGC TGTGCCCTTCT AGTTGCCAGC
CCTACTCCTG ATTTCCGGGC CGTCTAGACG ACACGGAAGA TCAACGGTCG

3851 CATCTGTTGT TTGCCCCCTCC CCCGTGCCTT CCTTGACCCT GGAAGGTGCC
GTAGACAACA AACGGGGAGG GGGCACGGAA GGAAC TGGGA CCTTCCACGG

3901 ACTCCCACTG TCCTTTCCTA ATAAAATGAG GAAATTGCAT CGCATTGTCT
TGAGGGTGAC AGGAAAGGAT TATTTTACTC CTTTAACGTA GCGTAACAGA

3951 GAGTAGGTGT CATTCTATTC TGGGGGGTGG GGTGGGGCAG GACAGCAAGG
CTCATCCACA GTAAGATAAG ACCCCCCACC CCACCCCGTC CTGTCTTCC

4001 GGGAGGATTG GGAAGACAAT AGCAGGCATG CTGGGGATGC GGTGGGCTCT
CCCTCCTAAC CCTTCTGTTA TCGTCCGTAC GACCCCTACG CCACCCGAGA

4051 ATGGCCGATC GCGCGCCGT ACTGAAATGT GTGGGCGTGG CTTAAGGGTG
TACCGGCTAG CCGCGCGGCA TGACTTTACA CACCCGCACC GAATTCCCAC

4101 GGAAAGAATA TATAAGGTGG GGTCTTATG TAGTTTTGTA TCTGTTTTGC
CCTTTCTTAT ATATTCCACC CCCAGAATAC ATCAAAACAT AGACAAAACG

4151 AGCAGCCGCC GCCGCCATGA GCACCAACTC GTTTGATGGA AGCATTGTGA
TCGTCCGGCG CGGCGGTACT CGTGGTTGAG CAAACTACCT TCGTAACACT

4201 GCTCATATTT GACAACGCGC ATGCCCCCAT GGGCCGGGGT GCGTCAGAA
CGAGTATAAA CTGTTGCGCG TACGGGGGTA CCCGGCCCCA CGCAGTCTTA

4251 GTGATGGGCT CCAGCATTGA TGGTCGCCCC GTCCTGCCCG CAAACTCTAC
CACTACCCGA GGTCGTAACCT ACCAGCGGGG CAGGACGGGC GTTTGAGATG

4301 TACCTTGACC TACGAGACCG TGTCTGGAAC GCCGTTGGAG ACTGCAGCCT
ATGGAAC TGG ATGCTCTGGC ACAGACCTTG CGGCAACCTC TGACGTCGGA

4351 CCGCCGCCGC TTCAGCCGCT GCAGCCACCG CCCGCGGGAT TGTGACTGAC
GGCGGCGGCG AAGTCGGCGA CGTCGGTGGC GGGCGCCCTA ACACTGACTG

4401 TTTGCTTTCC TGAGCCCGCT TGCAAACAGT GCAGCTTCCC GTTCATCCGC
AAACGAAAGG ACTCGGGCGA ACGTTTGTCA CGTCGAAGGG CAAGTAGGCG

4451 CCGCGATGAC AAGTTGACGG CTCTTTTGGC ACAATTGGAT TCTTTGACCC
GGCGCTACTG TTCAACTGCC GAGAAAACCG TGTTAACCTA AGAAACTGGG

4501 GGGAACTTAA TGTCGTTTCT CAGCAGCTGT TGGATCTGCG CCAGCAGGTT
CCCTTGAATT ACAGCAAAGA GTCGTCGACA ACCTAGACGC GGTCTGCCAA

4551 TCTGCCCTGA AGGCTTCCTC CCCTCCCAAT GCGGTTTAAA ACATAAATAA
AGACGGGACT TCCGAAGGAG GGGAGGGTTA CGCCAAATTT TGTATTTATT

4601 AAAACCAGAC TCTGTTTGA TTTGGATCAA GCAAGTGTCT TGCTGTCTTT
TTTTGGTCTG AGACAAACCT AAACCTAGTT CGTTCACAGA ACGACAGAAA

4651 ATTTAGGGGT TTTGCGCGCG CGGTAGGCCC GGGACCAGCG GTCTCGGTGC
TAAATCCCCA AAACGCGCGC GCCATCCGGG CCCTGGTCGC CAGAGCCAGC

Figure 26E

4751 GTTCAGATAC ATGGGCATAA GCCCGTCTCT GGGGTGGAGG TAGCACCACCT
CAAGTCTATG TACCCGTATT CGGGCAGAGA CCCCACCTCC ATCGTGGTGA

4801 GCAGAGCTTC ATGCTGCGGG GTGGTGTGTGT AGATGATCCA GTCGTAGCAG
CGTCTCGAAG TACGACGCCC CACCACAACA TCTACTAGGT CAGCATCGTC

4851 GAGCGCTGGG CGTGGTGCCT AAAAATGTCT TTCAGTAGCA AGCTGATTGC
CTCGCGACCC GCACCACGGA TTTTACAGA AAGTCATCGT TCGACTAACG

4901 CAGGGGCAGG CCCTTGGTGT AAGTGTTTAC AAAGCGGTTA AGCTGGGATG
GTCCCCGTCC GGGAAACCACA TTCACAAATG TTTCGCCAAT TCGACCCTAC

4951 GGTGCATACG TGGGGATATG AGATGCATCT TGGACTGTAT TTTTAGGTTG
CCACGTATGC ACCCCTATAC TCTACGTAGA ACCTGACATA AAAATCCAAC

5001 GCTATGTTCC CAGCCATATC CCTCCGGGGA TTCATGTTGT GCAGAACCAC
CGATACAAGG GTCGGTATAG GGAGGCCCCCT AAGTACAACA CGTCTTGGTG

5051 CAGCACAGTG TATCCGGTGC ACTTGGGAAA TTTGTCTATG AGCTTAGAAG
GTCGTGTCAC ATAGGCCACG TGAACCCTTT AAACAGTACA TCGAATCTTC

5101 GAAATGCGTG GAAGAACTTG GAGACGCCCT TGTGACCTCC AAGATTTTCC
CTTTACGCAC CTTCTTGAAC CTCTGCGGGA ACACTGGAGG TTCTAAAAGG

5151 ATGCATTCTG CCATAATGAT GGCAATGGGC CCACGGGCGG CGGCCTGGGC
TACGTAAGCA GGTATTACTA CCGTTACCCG GGTGCCCCGC GCCGGACCCG

5201 GAAGATATTT CTGGGATCAC TAACGTCATA GTTGTGTTCC AGGATGAGAT
CTTCTATAAA GACCCTAGTG ATTGCAGTAT CAACACAAGG TCCTACTCTA

5251 CGTCATAGGC CATTTTTACA AAGCGCGGGC GGAGGGTGCC AGACTGCGGT
GCAGTATCCG GTAAAAATGT TTCGCGCCCCG CCTCCCACGG TCTGACGCCA

5301 ATAATGGTTC CATCCGGCCC AGGGGCGTAG TTACCCTCAC AGATTTGCAT
TATTACCAAG GTAGGCCGGG TCCCCGCATC AATGGGAGTG TCTAAACGTA

5351 TTCCCACGCT TTGAGTTCAG ATGGGGGGAT CATGTCTACC TGCGGGGCGA
AAGGGTGCGA AACTCAAGTC TACCCCCCTA GTACAGATGG ACGCCCCGCT

5401 TGAAGAAAAC GGTTTCCGGG GTAGGGGAGA TCAGCTGGGA AGAAAGCAGG
ACTTCTTTTG CCAAAGGCC CATCCCCCTCT AGTCGACCCT TCTTTCGTCC

5451 TTCCTGAGCA GCTGCGACTT ACCGCAGCCG GTGGGCCCCG AAATCACACC
AAGGACTCGT CGACGCTGAA TGGCGTCGGC CACCCGGGCA TTTAGTGTGG

5501 TATTACCGGC TGCAACTGGT AGTTAAGAGA GCTGCAGCTG CCGTCATCCC
ATAATGGCCG ACGTTGACCA TCAATTCTCT CGACGTCGAC GGCAGTAGGG

5551 TGAGCAGGGG GGCCACTTCG TTAAGCATGT CCCTGACTCG CATGTTTTCC
ACTCGTCCCC CCGGTGAAGC AATTCGTACA GGGACTGAGC GTACAAAAGG

5601 CTGACCAAAT CCGCCAGAAG GCGCTCGCCG CCCAGCGATA GCAGTTCTTG
GACTGGTTTA GGCGGTCTTC CGCGAGCGGC GGGTCGCTAT CGTCAAGAAC

Figure 26 F

5701 TTTTGAGCGT TTGACCAAGC AGTTCAGGC GGTCCCACAG CTCGGTCACC
AAAACTCGCA AACTGGTTCG TCAAGGTCCG CCAGGGTGTC GAGCCAGTGG

5751 TGCTCTACGG CATCTCGATC CAGCATATCT CCTCGTTTCG CGGGTTGGGG
ACGAGATGCC GTAGAGCTAG GTCGTATAGA GGAGCAAAGC GCCCAACCCC

5801 CGGCTTTTCG TGTACGGCAG TAGTCGGTGC TCGTCCAGAC GGGCCAGGGT
GCCGAAAGCG ACATGCCGTC ATCAGCCACG AGCAGGTCTG CCCGGTCCCA

5851 CATGTCTTTC CACGGGCGCA GGGTCCTCGT CAGCGTAGTC TGGGTACGG
GTACAGAAAG GTGCCCGCGT CCCAGGAGCA GTCGCATCAG ACCCAGTGCC

5901 TGAAGGGGTG CGCTCCGGGC TGC GCGCTGG CCAGGGTGCG CTTGAGGCTG
ACTTCCCCAC GCGAGGCCCG ACGCGCGACC GGTCCCACGC GAACTCCGAC

5951 GTCTTGCTGG TGCTGAAGCG CTGCCGGTCT TCGCCCTGCG CGTCGGCCAG
CAGGACGACC ACGACTTCGC GACGGCCAGA AGCGGGACGC GCAGCCGGTC

6001 GTAGCATTTG ACCATGGTGT CATAGTCCAG CCCCTCCGCG GCGTGGCCCT
CATCGTAAAC TGGTACCACA GTATCAGGTC GGGGAGGCGC CGCACC GGGA

6051 TGGCGCGCAG CTTGCCCTTG GAGGAGGCGC CGCACGAGGG GCAGTGCAGA
ACCGCGCGTC GAACGGGAAC CTCTCCGCG GCGTGCTCCC CGTCACGTCT

6101 CTTTGTAGGG CGTAGAGCTT GGGCGCGAGA AATACCGATT CCGGGGAGTA
GAAACTCCC GCATCTCGAA CCCGCGCTCT TTATGGCTAA GGCCCCCTCAT

6151 GGCATCCGCG CCGCAGGCC CCGCAGACGGT CTCGCATTCC ACGAGCCAGG
CCGTAGGCGC GCGTCCGGG GCGTCTGCCA GAGCGTAAGG TGCTCGGTCC

6201 TGAGCTCTGG CCGTTCGGGG TCAAAAACCA GGTTTCCCC ATGCTTTTTG
ACTCGAGACC GGCAAGCCCC AGTTTTTGGT CCAAAGGGGG TACGAAAAAC

6251 ATGCGTTTCT TACCTCTGGT TTCCATGAGC CCGTGTCCAC GCTCGGTGAC
TACGCAAAGA ATGGAGACCA AAGGTACTCG GCCACAGGTG CGAGCCACTG

6301 GAAAAGGCTG TCCGTGTCCC CGTATACAGA CTTGAGAGGC CTGTCTCTGA
CTTTTCCGAC AGGCACAGGG GCATATGTCT GAACTCTCCG GACAGGAGCT

6351 GCGGTGTTCC GCGGTCTTCC TCGTATAGAA ACTCGGACCA CTCTGAGACA
CGCCACAAGG CGCCAGGAGG AGCATATCTT TGAGCCTGGT GAGACTCTGT

6401 AAGGCTCGCG TCCAGGCCAG CACGAAGGAG GCTAAGTGGG AGGGGTAGCG
TTCCGAGCGC AGGTCCGGTC GTGCTTCCTC CGATTACCC TCCCCATCGC

6451 GTCGTTGTCC ACTAGGGGGT CCACTCGCTC CAGGGTGTGA AGACACATGT
CAGCAACAGG TGATCCCCCA GGTGAGCGAG GTCCCACT TCTGTGTACA

6501 CGCCCTCTTC GGCATCAAGG AAGGTGATTG GTTTGTAGGT GTAGGCCACG
GCGGGAGAAG CCGTAGTTCC TTCCACTAAC CAAACATCCA CATCCGGTGC

6551 TGACCGGGTG TTCCTGAAGG GGGGCTATAA AAGGGGGTGG GGGCGCGTTC
ACTGGCCAC AAGGACTTCC CCCC GATATT TTCCCCACC CCCGCGCAAG

Figure 266

6651 AGTACTCCCT CTGAAAAGCG GGCATGACTT CTGCGCTAAG ATTGTCAGTT
 TCATGAGGGA GACTTTTCGC CCGTACTGAA GACGCGATTG TAACAGTCAA
 6701 TCCAAAAACG AGGAGGATTT GATATTCACC TGGCCCGCGG TGATGCCTTT
 AGGTTTTTGC TCCTCCTAAA CTATAAGTGG ACCGGGCGCC ACTACGGAAA
 6751 GAGGGTGGCC GCATCCATCT GGTCAAGAAA GACAATCTTT TTGTTGTCAA
 CTCCCACCGG CGTAGGTAGA CCAGTCTTTT CTGTTAGAAA AACAAACAGTT
 6801 GCTTGGTGGC AAACGACCCG TAGAGGGCGT TGGACAGCAA CTTGGCGATG
 CGAACCACCG TTTGCTGGGC ATCTCCCGCA ACCTGTCGTT GAACCGCTAC
 6851 GAGCGCAGGG TTTGGTTTTT GTCGCGATCG GCGCGCTCCT TGGCCGCGAT
 CTCGCGTCCC AAACCAAAAA CAGCGCTAGC GCGCGAGGA ACCGGCGCTA
 6901 GTTTAGCTGC ACGTATTCGC GCGCAACGCA CCGCCATTCT GGAAAGACGG
 CAAATCGACG TGCATAAGCG CGCGTTGCGT GGCGGTAAGC CCTTCTGCC
 6951 TGGTGCCTC GTCGGGCACC AGGTGCACGC GCCAACCGCG GTTGTGCAGG
 ACCACGCGAG CAGCCCGTGG TCCACGTGCG CGGTGGGCGC CAACACGTCC
 7001 GTGACAAGGT CAACGCTGGT GGCTACCTCT CCGCGTAGGC GCTCGTTGGT
 CACTGTTCCA GTTGCACCA CCGATGGAGA GGCGCATCCG CGAGCAACCA
 7051 CCAGCAGAGG CGGCCGCCCT TGC GCGAGCA GAATGGCGGT AGGGGGTCTA
 GGTCGTCTCC GCCGGCGGGA ACGCGCTCGT CTTACCGCCA TCCCCAGAT
 7101 GCTGCGTCTC GTCCGGGGGG TCTGCGTCCA CGGTAAAGAC CCCGGGCAGC
 CGACGCAGAG CAGGCCCCC AGACGCAGGT GCCATTCTG GGGCCCCGTCG
 7151 AGGCGCGCGT CGAAGTAGTC TATCTTGCAT CCTTGCAAGT CTAGCGCCTG
 TCCGCGCGCA GCTTCATCAG ATAGAACGTA GGAACGTTCA GATCGCGGAC
 7201 CTGCCATGCG CGGGCGGCAA GCGCGCGCTC GTATGGGTTG AGTGGGGGAC
 GACGGTACGC GCCCGCCGTT CGCGCGCGAG CATACCCAAC TCACCCCTG
 7251 CCCATGGCAT GGGGTGGGTG AGCGCGGAGG CGTACATGCC GCAAATGTGCG
 GGGTACCGTA CCCCACCCAC TCGCGCCTCC GCATGTACGG CGTTTACAGC
 7301 TAAACGTAGA GGGGCTCTCT GAGTATTCCA AGATATGTAG GGTAGCATCT
 ATTTGCATCT CCCCAGAGAG CTCATAAGGT TCTATACATC CCATCGTAGA
 7351 TCCACCGCGG ATGCTGGCGC GCACGTAATC GTATAGTTG TGCGAGGGAG
 AGGTGGCGCC TACGACCGCG CGTGCAATTAG CATATCAAGC ACGCTCCCTC
 7401 CGAGGAGGTC GGGACCGAGG TTGCTACGGG CGGGCTGCTC TGCTCGGAAG
 GCTCCTCCAG CCCTGGCTCC AACGATGCCC GCCCGACGAG ACGAGCCTTC
 7451 ACTATCTGCC TGAAGATGGC ATGTGAGTTG GATGATATGG TTGGACGCTG
 TGATAGACGG ACTTCTACCG TACACTCAAC CTACTATACC AACCTGCGAC
 7501 GAAGACGTTG AAGCTGGCGT CTGTGAGACC TACCGCGTCA CGCACGAAGG
 CTTCTGCAAC TTCGACCGCA GACACTCTGG ATGGCGCAGT GCGTGCTTCC

Figure 26 H

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7601  TCTAGGGCGC AGTAGTCCAG GGTTCCTTG ATGATGTCAT ACTTATCCTG
      AGATCCCCGC TCATCAGGTC CCAAAGGAAC TACTACAGTA TGAATAGGAC

7651  TCCCTTTTTT TTCCACAGCT CGCGGTTGAG GACAAACTCT TCGCGGTCTT
      AGGGAAAAAA AAGGTGTCGA GCGCCAACTC CTGTTTGAGA AGCGCCAGAA

7701  TCCAGTACTC TTGGATCGGA AACCCGTCGG CCTCCGAACG GTAAGAGCCT
      AGGTCATGAG AACCTAGCCT TTGGGCAGCC GGAGGCTTGC CATTCCTCGGA

7751  AGCATGTAGA ACTGGTTGAC GGCCTGGTAG GCGCAGCATC CCTTTTCTAC
      TCGTACATCT TGACCAACTG CCGGACCATC CGCGTCGTAG GGAAAAGATG

7801  GGGTAGCGCG TATGCCTGCG CGGCCTTCCG GAGCGAGGTG TGGGTGAGCG
      CCCATCGCGC ATACGGACGC GCCGGAAGGC CTCGCTCCAC ACCCACTCGC

7851  CAAAGGTGTC CCTGACCATG ACTTTGAGGT ACTGGTATTT GAAGTCAGTG
      GTTTCACAG GGACTGGTAC TGAAACTCCA TGACCATAAA CTTCACTCAG

7901  TCGTCGCATC CGCCCTGCTC CCAGAGCAAA AAGTCCGTGC GCTTTTGGGA
      AGCAGCGTAG GCGGGACGAG GGTCTCGTTT TTCAGGCACG CGAAAAACCT

7951  ACGCGGATTT GGCAGGGCGA AGGTGACATC GTTGAAGAGT ATCTTTCCCG
      TGCGCCTAAA CCGTCCCGCT TCCACTGTAG CAACTTCTCA TAGAAAGGGC

8001  CGCGAGGCAT AAAGTTGCGT GTGATGCGGA AGGGTCCCCG CACCTCGGAA
      GCGCTCCGTA TTCAACGCA CACTACGCCT TCCCAGGGCC GTGGAGCCTT

8051  CGGTTGTTAA TTACCTGGGC GCGGAGCACG ATCTCGTCAA AGCCGTTGAT
      GCCAACAATT AATGGACCCG CCGCTCGTGC TAGAGCAGTT TCGGCAACTA

8101  GTTGTGGCCC ACAATGTAAA GTTCCAAGAA GCGCGGGATG CCCTTGATGG
      CAACACCGGG TGTTACATTT CAAGGTTCTT CGCGCCCTAC GGGAACTACC

8151  AAGGCAATTT TTTAAGTTCC TCGTAGGTGA GCTCTTCAGG GGAGCTGAGC
      TTCCGTAAAA AAATTCAAGG AGCATCCACT CGAGAAGTCC CCTCGACTCG

8201  CCGTGCTCTG AAAGGGCCCA GTCTGCAAGA TGAGGGTTGG AAGCGACGAA
      GGCACGAGAC TTTCCCGGGT CAGACGTTCT ACTCCCAACC TTCGTGCTTT

8251  TGAGCTCCAC AGGTCACGGG CCATTAGCAT TTGCAGGTGG TCGCGAAAGG
      ACTCGAGGTG TCCAGTGCCC GGTAATCGTA AACGTCCACC AGCGCTTTCC

8301  TCCTAAACTG GCGACCTATG GCCATTTTTT CTGGGGTGAT GCAGTAGAAG
      AGGATTTGAC CGCTGGATAC CGGTAAAAAA GACCCCACTA CGTCATCTTC

8351  GTAAGCGGGT CTTGTTCCCA GCGGTCCCAT CCAAGGTTTC CGGCTAGGTC
      CATTCGCCCC GAACAAGGGT CGCCAGGGTA GGTTCCAAGC GCCGATCCAG

8401  TCGCGCGGCA GTCAGTAGAG GCTCATCTCC GCCGAACTTC ATGACCAGCA
      AGCGCGCCGT CAGTGATCTC CGAGTAGAGG CGGCTTGAAG TACTGGTCGT

8451  TGAAGGGCAC GAGCTGCTTC CCAAAGGCCC CCATCCAAGT ATAGGTCTCT
      ACTTCCCGTG CTCGACGAAG GGTTCCTGGG GGTAGGTTCA TATCCAGAGA

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Figure 26I

8551 GAAGAACTGG ATCTCCCGCC ACCAATTGGA GGAGTGGCTA TTGATGTGGT
 CTTCTTGACC TAGAGGGCGG TGGTTAACCT CCTCACCAGT AACTACACCA

 8601 GAAAGTAGAA GTCCCTGCGA CGGGCCGAAC ACTCGTGCTG GCTTTTGTAA
 CTTTCATCTT CAGGGACGCT GCCCGGCTTG TGAGCACGAC CGAAAACATT

 8651 AAACGTGCGC AGTACTGGCA GCGGTGCACG GGCTGTACAT CCTGCACGAG
 TTTGCACGCG TCATGACCGT CGCCACGTGC CCGACATGTA GGACGTGCTC

 8701 GTTGACCTGA CGACCGCGCA CAAGGAAGCA GAGTGGGAAT TTGAGCCCCCT
 CAACTGGACT GCTGGCGCGT GTTCCTTCGT CTCACCCTTA AACTCGGGGA

 8751 CGCCTGGCGG GTTTGGCTGG TGGTCTTCTA CTTTCGGCTGC TTGTCCTTGA
 GCGGACCGCC CAAACCGACC ACCAGAAGAT GAAGCCGACG AACAGGAACT

 8801 CCGTCTGGCT GCTCGAGGGG AGTTACGGTG GATCGGACCA CCACGCCGCG
 GGCAGACCGA CGAGCTCCCC TCAATGCCAC CTAGCCTGGT GGTGCGGCGC

 8851 CGAGCCCCAA GTCCAGATGT CCGCGCGCGG CGGTCGGAGC TTGATGACAA
 GCTCGGGTTT CAGGTCTACA GCGCGCGGCC GCCAGCCTCG AACTACTGTT

 8901 CATCGCGCAG ATGGGAGCTG TCCATGGTCT GGAGCTCCCG CGGCGTCAGG
 GTAGCGCGTC TACCCTCGAC AGGTACCAGA CCTCGAGGGC GCCGCACTCC

 8951 TCAGGCGGGA GCTCCTGCAG GTTTACCTCG CATAGACGGG TCAGGGCGCG
 AGTCCGCCCT CGAGGACGTC CAAATGGAGC GTATCTGCCC AGTCCCGCGC

 9001 GGCTAGATCC AGGTGATACC TAATTTCCAG GGGCTGGTTG GTGGCGGCGT
 CCGATCTAGG TCCACTATGG ATTAAAGGTC CCCGACCAAC CACCGCCGCA

 9051 CGATGGCTTG CAAGAGGCCG CATCCCCGCG GCGCGACTAC GGTACCGCGC
 GCTACCGAAC GTTCTCCGGC GTAGGGGCGC CGCGCTGATG CCATGGCGCG

 9101 GGCGGGCGST GGGCCGCGGG GGTGTCCTTG GATGATGCAT CTAAGAGCGG
 CCGCCGCCA CCCGGCGCCC CCACAGGAAC CTACTACGTA GATTTTCGCC

 9151 TGACGCGGGC GAGCCCCCGG AGGTAGGGGG GGCTCCGGAC CCGCCGGGAG
 ACTGCGCCCG CTCGGGGGCC TCCATCCCCC CCGAGGCCTG GCGGGCCCTC

 9201 AGGGGGCAGG GGCACGTCGG CGCCGCGCGC GGGCAGGAGC TGGTGCTGCG
 TCCCCGTCC CCGTGCAGCC GCGGCGCGCG CCCGTCCTCG ACCACGACGC

 9251 CGCGTAGGTT GCTGGCGAAC GCGACGACGC GGCGGTTGAT CTCCTGAATC
 GCGCATCCAA CGACCGCTTG CGCTGCTGCG CCGCCAATA GAGGACTTAG

 9301 TGGCGCCTCT GCGTGAAGAC GACGGGCCCC GTGAGCTTGA ACCTGAAAGA
 ACCGCGGAGA CGCACTTCTG CTGCCCCGGC CACTCGAACT TGGACTTTCT

 9351 GAGTTCGACA GAATCAATTT CGGTGTCGTT GACGGCGGCC TGGCGCAAAA
 CTCAAGCTGT CTTAGTTAAA GCCACAGCAA CTGCCGCCGG ACCGCGTTTT

 9401 TCTCCTGCAC GTCTCCTGAG TTGTCTTGAT AGGCGATCTC GGCCATGAAC
 AGAGGACGTG CAGAGGACTC AACAGAACTA TCCGCTAGAG CCGGTACTTG

Figure 26 J

9501 GCGGCGGAGG TCGTTGGAAA TCGGGGCCAT GAGCTGCGAG AAGGCGTTGA
CCGCCGCTCC AGCAACCTTT ACGCCCGGTA CTCGACGCTC TTCCGCAACT

9551 GGCCTCCCTC GTTCCAGACG CGGCTGTAGA CCACGCCCCC TTCGGCATCG
CCGGAGGGAG CAAGGTCTGC GCCGACATCT GGTGCGGGGG AAGCCGTAGC

9601 CGGGCGCGCA TGACCACCTG CGCGAGATTG AGCTCCACGT GCCGGGCGAA
GCCCCGCGGT ACTGGTGGAC GCGCTCTAAC TCGAGGTGCA CGGCCCCGCTT

9651 GACGGCGTAG TTTCGCAGGC GCTGAAAGAG GTAGTTGAGG GTGGTGGCGG
CTGCCGCATC AAAGCGTCCG CGACTTTCTC CATCAACTCC CACCACCGCC

9701 TGTGTTCTGC CACGAAGAAG TACATAACCC AGCGTCGCAA CGTGGATTTCG
ACACAAGACG GTGCTTCTTC ATGTATTGGG TCGCAGCGTT GCACCTAAGC

9751 TTGATATCCC CCAAGGCCCTC AAGGCGCTCC ATGGCCTCGT AGAAGTCCAC
AACTATAGGG GGTTCGGAG TTCCGCGAGG TACCGGAGCA TCTTCAGGTG

9801 GGCGAAGTTG AAAAAGTGGG AGTTGCGCGC CGACACGGTT AACTCCTCCT
CCGCTTCAAC TTTTGGACCC TCAACGCGCG GCTGTGCCAA TTGAGGAGGA

9851 CCAGAAGACG GATGAGCTCG GCGACAGTGT CGCGCACCTC GCGCTCAAAG
GGTCTTCTGC CTACTCGAGC CGCTGTCACA GCGCGTGGAG CGCGAGTTTC

9901 GCTACAGGGG CCTCTTCTTC TTCTTCAATC TCCTCTTCCA TAAGGGCCTC
CGATGTCCCC GGAGAAGAAG AAGAAGTTAG AGGAGAAGGT ATTCCCGGAG

9951 CCCTTCTTCT TCTTCTGGCG GCGGTGGGGG AGGGGGGACA CGGCGGCGAC
GGGAAGAAGA AGAAGACCGC CGCCACCCCC TCCCCCTGT GCCGCCGCTG

10001 GACGGCGCAC CGGGAGGCGG TCGACAAAGC GCTCGATCAT CTCCCCGCGG
CTGCCGCGTG GCCCTCCGCC AGCTGTTTCG CGAGCTAGTA GAGGGGCGCC

10051 CGACGGCGCA TGGTCTCGGT GACGGCGCGG CCGTCTCGC GGGGGCGCAG
GCTGCCGCGT ACCAGAGCCA CTGCCGCGCC GGCAAGAGCG CCCCCGCGTC

10101 TTGGAAGACG CCGCCCGTCA TGTCCCGGTT ATGGGTTGGC GGGGGGCTGC
AACC'TTCTGC GCGGGGCAGT ACAGGGCCAA TACCCAACCG CCCCCGACG

10151 CATGCGGCAG GGATACGGCG CTAACGATGC ATCTCAACAA TTGTTGTGTA
GTACGCCGTC CCTATGCCGC GATTGCTACG TAGAGTTGTT AACAACACAT

10201 GGTACTCCGC CGCCGAGGGA CCTGAGCGAG TCCGCATCGA CCGGATCGGA
CCATGAGGCG GCGGCTCCCT GGACTCGCTC AGGCGTAGCT GGCCTAGCCT

10251 AAACCTCTCG AGAAAGGCGT CTAACCAGTC ACAGTCGCAA GGTAGGCTGA
TTTGGAGAGC TCTTTCGCA GATTGGTCAG TGTCAGCGTT CCATCCGACT

10301 GCACCGTGCG GGGCGGCAGC GGGCGGCGGT CGGGGTTGTT TCTGGCGGAG
CGTGGCACCG CCCGCCGTCG CCCGCCGCA GCCCAACAA AGACCGCCTC

10351 GTGCTGCTGA TGATGTAATT AAAGTAGGCG GTCTTGAGAC GCGGATGGT
CACGACGACT ACTACATTAA TTTCATCCGC CAGAACTCTG CCGCCTACCA

Figure 26 K

10451	CGGCCATGCC	CCAGGCTTCG	TTTGTACATC	GGCGCAGGTC	TTTGTAGTAG
	GCCGGTACGG	GGTCCGAAGC	AAAACGTAG	CCGCGTCCAG	AAACATCATC
10501	TCTTGCATGA	GCCTTTCTAC	CGGCACTTCT	TCTTCTCCTT	CCTCTTGTCC
	AGAACGTACT	CGGAAAGATG	GCCGTGAAGA	AGAAGAGGAA	GGAGAACAGG
10551	TGCATCTCTT	GCATCTATCG	CTGCGGCGGC	GGCGGAGTTT	GGCCGTAGGT
	ACGTAGAGAA	CGTAGATAGC	GACGCCGCCG	CCGCCTCAAA	CCGGCATCCA
10601	GGCGCCCTCT	TCCTCCCATG	CGTGTGACCC	CGAAGCCCCCT	CATCGGCTGA
	CCGCGGGAGA	AGGAGGGTAC	GCACACTGGG	GCTTCGGGGA	GTAGCCGACT
10651	AGCAGGGCTA	GGTCGGCGAC	AACGCGCTCG	GCTAATATGG	CCTGCTGCAC
	TCGTCCCGAT	CCAGCCGCTG	TTGCGCGAGC	CGATTATACC	GGACGACGTG
10701	CTGCGTGAGG	GTAGACTGGA	AGTCATCCAT	GTCCACAAAG	CGGTGGTATG
	GACGCACTCC	CATCTGACCT	TCAGTAGGTA	CAGGTGTTTC	GCCACCATAC
10751	CGCCCGTGTT	GATGGTGTA	GTGCAGTTGG	CCATAACGGA	CCAGTTAACG
	GCGGGCACAA	CTACCACATT	CACGTCAACC	GGTATTGCCT	GGTCAATTGC
10801	GTCTGGTGAC	CCGGCTGCGA	GAGCTCGGTG	TACCTGAGAC	GCGAGTAAGC
	CAGACCACTG	GGCCGACGCT	CTCGAGCCAC	ATGGACTCTG	CGCTCATTCG
10851	CCTCGAGTCA	AATACGTAGT	CGTTGCAAGT	CCGCACCAGG	TACTGGTATC
	GGAGCTCAGT	TTATGCATCA	GCAACGTTCA	GGCGTGGTCC	ATGACCATAG
10901	CCACCAAAAA	GTGCGGCGGC	GGCTGGCGGT	AGAGGGGCCA	GCGTAGGGTG
	GGTGGTTTTT	CACGCCGCCG	CCGACCGCCA	TCTCCCCGGT	CGCATCCCAC
10951	GCCGGGGCTC	CGGGGGCGAG	ATCTTCCAAC	ATAAGGCGAT	GATATCCGTA
	CGGCCCCGAG	GCCCCCGCTC	TAGAAGGTTG	TATTCCGCTA	CTATAGGCAT
11001	GATGTACCTG	GACATCCAGG	TGATGCCGGC	GGCGGTGGTG	GAGGCGCGCG
	CTACATGGAC	CTGTAGGTCC	ACTACGGCCG	CCGCCACCAC	CTCCGCGCGC
11051	GAAAGTCGCG	GACGCGGTTT	CAGATGTTGC	GCAGCGGCAA	AAAGTGCTCC
	CTTTCAGCGC	CTGCGCCAAG	GTCTACAACG	CGTCGCCGTT	TTTCACGAGG
11101	ATGGTCGGGA	CGCTCTGGCC	GGTCAGGCGC	GCGCAATCGT	TGACGCTCTA
	TACCAGCCCT	GCGAGACCGG	CCAGTCCGCG	CGCGTTAGCA	ACTGCGAGAT
11151	GACCGTGCAA	AAGGAGAGCC	TGTAAGCGGG	CACTCTTCCG	TGGTCTGGTG
	CTGGCACGTT	TTCTCTCTCG	ACATTGCCCC	GTGAGAAGGC	ACCAGACCAC
11201	GATAAATTCG	CAAGGGTATC	ATGGCGGACG	ACCGGGGTTC	GAGCCCCGTA
	CTATTTAAGC	GTTCCTCATAG	TACCGCCTGC	TGGCCCCAAG	CTCGGGGCAT
11251	TCCGGCCGTC	CGCCGTGATC	CATGCGGTTA	CCGCCCGCGT	GTCGAACCCA
	AGGCCGGCAG	GCGGCACTAG	GTACGCCAAT	GGCGGGCGCA	CAGCTTGGGT
11301	GGTGTGCGAC	GTCAGACAAC	GGGGGAGTGC	TCCTTTTGGC	TTCTTCCAG
	CCACACGCTG	CAGTCTGTTG	CCCCCTCACG	AGGAAAACCG	AAGGAAGGTG

Figure 26L

11401 AAGCGGTTAG GCTGGAAAGC GAAAGCATT AAGTGGCTCGC TCCCTGTAGC
TTCGCCAATC CGACCTTTTCG CTTTCGTAAT TCACCGAGCG AGGGACATCG

11451 CGGAGGGTTA TTTTCCAAGG GTTGAGTCGC GGGACCCCCG GTTCGAGTCT
GCCTCCCAAT AAAAGGTTCC CAACTCAGCG CCCTGGGGGC CAAGCTCAGA

11501 CGGACCGGCC GGAATGCGGC GAACGGGGGT TTGCCTCCCC GTCATGCAAG
GCCTGGCCGG CCTGACGCCG CTTGCCCCCA AACGGAGGGG CAGTACGTTT

11551 ACCCCGCTTG CAAATTCCTC CGGAAACAGG GACGAGCCCC TTTTTTGCTT
TGGGGCGAAC GTTTAAGGAG GCCTTTGTCC CTGCTCGGGG AAAAAACGAA

11601 TTCCCAGATG CATCCGGTGC TGCGGCAGAT GCGCCCCCTT CCTCAGCAGC
AAGGGTCTAC GTAGGCCACG ACGCCGTCTA CGCGGGGGGA GGAGTCGTGC

11651 GGCAAGAGCA AGAGCAGCGG CAGACATGCA GGGCACCTTC CCCTCCTCCT
CCGTTCTCGT TCTCGTCGCC GTCTGTACGT CCCGTGGGAG GGGAGGAGGA

11701 ACCGCGTCAG GAGGGGCGAC ATCCGCGGTT GACGCGGCAG CAGATGGTGA
TGGCGCAGTC CTCCCCGCTG TAGGCGCCAA CTGCGCCGTC GTCTACCACT

11751 TTACGAACCC CCGCGGCGCC GGGCCCGGCA CTACCTGGAC TTGGAGGAGG
AATGCTTGGG GGCGCCGCGG CCCGGGCCGT GATGGACCTG AACCTCCTCC

11801 GCGAGGGCCT GGCGCGGCTA GGAGCGCCCT CTCCTGAGCG GCACCCAAGG
CGCTCCCGGA CCGCGCCGAT CCTCGCGGGA GAGGACTCGC CGTGGGTTC

11851 GTGCAGCTGA AGCGTGATAC GCGTGAGGCG TACGTGCCGC GGCAGAACCT
CACGTCGACT TCGCACTATG CGCACTCCGC ATGCACGGCG CCGTCTTGGA

11901 GTTTCGCGAC CGCGAGGGAG AGGAGCCCGA GGAGATGCGG GATCGAAAGT
CAAAGCGCTG GCGCTCCCTC TCCTCGGGCT CCTCTACGCC CTAGCTTTCA

11951 TCCACGCAGG GCGCGAGCTG CGGCATGGCC TGAATCGCGA GCGGTTGCTG
AGGTGCGTCC CGCGCTCGAC GCCGTACCGG ACTTAGCGCT CGCCAACGAC

12001 CGCGAGGAGG ACTTTGAGCC CGACGCGCGA ACCGGGATTA GTCCCGCGCG
GCGTCTCTCC TGAAACTCGG GCTGCGCGCT TGGCCCTAAT CAGGGCGCGC

12051 CGCACACGTG GCGGCCGCGG ACCTGGTAAC CGCATAAGAG CAGACGGTGA
GCGTGTCAC CGCCGGCGGC TGGACCATG GCGTATGCTC GTCTGCCACT

12101 ACCAGGAGAT TAACTTTCAA AAAAGCTTTA ACAACCACGT GCGTACGCTT
TGGTCTCTA ATTGAAAGTT TTTTCGAAAT TGTTGGTGCA CGCATGCGAA

12151 GTGGCGCGCG AGGAGGTGGC TATAGGACTG ATGCATCTGT GGGACTTTGT
CACCAGCGCG TCCTCCACCG ATATCCTGAC TACGTAGACA CCCTGAAACA

12201 AAGCGCGCTG GAGCAAAACC CAAATAGCAA GCCGCTCATG GCGCAGCTGT
TTCGCGCGAC CTCGTTTTGG GTTTATCGTT CGGCGAGTAC CGCGTCGACA

12251 TCCTTATAGT GCAGCACAGC AGGGACAACG AGGCATTGAG GGATGCGCTG
AGGAATATCA CGTCGTGTGC TCCCTGTTGC TCCGTAAGTC CCTACGCGAC

Figure 26 M

12351 CCTGCAGAGC ATAGTGGTGC AGGAGCGCAG CTTGAGCCTG GCTGACAAGG
GGACGTCTCG TATCACCACG TCCTCGCGTC GAACTCGGAC CGACTGTTCC

12401 TGGCCGCCAT CAACTATTCC ATGCTTAGCC TGGGCAAGTT TTACGCCCCG
ACCGGCGGTA GTTGATAAGG TACGAATCGG ACCCGTTCAA AATGCGGGCG

12451 AAGATATAACC ATACCCCTTA CGTTCCCATA GACAAGGAGG TAAAGATCGA
TTCTATATGG TATGGGGAAT GCAAGGGTAT CTGTTCTCTC ATTTCTAGCT

12501 GGGGTTCTAC ATGCGCATGG CGCTGAAGGT GCTTACCTTG AGCGACGACC
CCCCAAGATG TACGCGTACC GCGACTTCCA CGAATGGAAC TCGCTGCTGG

12551 TGGGCGTTTA TCGCAACGAG CGCATCCACA AGGCCGTGAG CGTGAGCCGG
ACCCGCAAAT AGCGTTGCTC GCGTAGGTGT TCCGGCACTC GCACTCGGCC

12601 CGGCGCGAGC TCAGCGACCG CGAGCTGATG CACAGCCTGC AAAGGGCCCT
GCCGCGCTCG AGTCGCTGGC GCTCGACTAC GTGTCGGACG TTTCCCGGGA

12651 GGCTGGCACG GGCAGCGGCG ATAGAGAGGC CGAGTCCTAC TTTGACGCGG
CCGACCGTGC CCGTCGCGC TATCTCTCCG GCTCAGGATG AAATGCGCC

12701 GCGCTGACCT GCGCTGGGCC CCAAGCCGAC GCGCCCTGGA GGCAGCTGGG
CGCGACTGGA CGCGACCCGG GGTTCGGCTG CGCGGGACCT CCGTCGACCC

12751 GCCGGACCTG GGCTGGCGGT GGCACCCGCG CGCGCTGGCA ACGTCGGCGG
CGGCCTGGAC CCGACCGCCA CCGTGGGCGC GCGCGACCGT TGCAGCCGCC

12801 CGTGGAGGAA TATGACGAGG ACGATGAGTA CGAGCCAGAG GACGGCGAGT
GCACCTCCTT ATACTGCTCC TGCTACTCAT GCTCGGTCTC CTGCCGCTCA

12851 ACTAAGCGGT GATGTTTCTG ATCAGATGAT GCAAGACGCA ACGGACCCGG
TGATTGCGCA CTACAAAGAC TAGTCTACTA CGTTCTGCGT TGCCTGGGCC

12901 CGGTGCGGGC GGCCTGTCAG AGCCAGCCGT CCGGCCTTAA CTCCACGGAC
GCCACGCCCC CCGCGACGTC TCGGTCGGCA GGCCGGAATT GAGGTGCCTG

12951 GACTGGCGCC AGGTCATGGA CCGCATCATG TCGCTGACTG CGCGCAATCC
CTGACCGCGG TCCAGTACCT GGCCTAGTAC AGCGACTGAC GCGCGTTAGG

13001 TGACGCGTTC CGGCAGCAGC CGCAGGCCAA CCGGCTCTCC GCAATTCTGG
ACTGCGCAAG GCCGTCGTCG GCGTCCGGTT GGCCGAGAGG CGTTAAGACC

13051 AAGCGGTGGT CCCGGCGCGC GCAAACCCCA CGCACGAGAA GGTGCTGGCG
TTCGCCACCA GGGCCGCGCG CGTTTGGGGT GCGTGCTCTT CCACGACCGC

13101 ATCGTAAACG CGCTGGCCGA AAACAGGGCC ATCCGGCCCG ACGAGGCCGG
TAGCATTTGC GCGACCGGCT TTTGTCCCGG TAGGCCGGGC TGCTCCGGCC

13151 CCTGGTCTAC GACGCGCTGC TTCAGCGCGT GGCTCGTTAC AACAGCGGCA
GGACCAGATG CTGCGCGACG AAGTCGCGCA CCGAGCAATG TTGTCGCCGT

13201 ACGTGCAGAC CAACCTGGAC CGGCTGGTGG GGGATGTGCG CGAGGCCGTG
TGCACGTCTG GTTGGACCTG GCCGACCACC CCCTACACGC GCTCCGGCAC

Figure 26 N

13301 ACTAAACGCC TTCCTGAGTA CACAGCCCCG CAACGTGCCG CGGGGACAGG
TGATTTGCGG AAGGACTCAT GTGTCGGGCG GTTGACACGC GCCCCTGTCC

13351 AGGACTACAC CAACTTTGTG AGCGCACTGC GGCTAATGGT GACTGAGACA
TCCTGATGTG GTTGAAACAC TCGCGTGACG CCGATTACCA CTGACTCTGT

13401 CCGCAAAGTG AGGTGTACCA GTCTGGGCCA GACTATTTTT TCCAGACCAG
GGCGTTTCAC TCCACATGGT CAGACCCGGT CTGATAAAAA AGGTCCTGGTC

13451 TAGACAAGGC CTGCAGACCG TAAACCTGAG CCAGGCTTTC AAAAAGTTGC
ATCTGTTCCG GACGTCTGGC ATTTGGACTC GGTCCGAAAG TTTTGAACG

13501 AGGGGCTGTG GGGGGTGCGG GCTCCCACAG GCGACCGCGC GACCGTGTCT
TCCCCGACAC CCCCCACGCC CGAGGGTGTC CGCTGGCGCG CTGGCACAGA

13551 AGCTTGCTGA CGCCCAACTC GCGCCTGTTG CTGCTGCTAA TAGCGCCCTT
TCGAACGACT GCGGGTTGAG CCGGACAAAC GACGACGATT ATCGCGGGAA

13601 CACGGACAGT GGCAGCGTGT CCCGGGACAC ATACCTAGGT CACTTGCTGA
GTGCTGTCA CCGTCGCACA GGGCCTGTG TATGGATCCA GTGAACGACT

13651 CACTGTACCG CGAGGCCATA GGTCAGGCGC ATGTGGACGA GCATACTTTC
GTGACATGGC GCTCCGGTAT CCAGTCCGCG TACACCTGCT CGTATGAAAG

13701 CAGGAGATTA CAAGTGTCAG CCGCGCGCTG GGGCAGGAGG ACACGGGCGAG
GTCTCTAAT GTTCACAGTC GGCAGCGGAC CCCGTCTCTC TGTGCCCCGC

13751 CCTGGAGGCA ACCCTAAACT ACCTGCTGAC CAACCGGCGG CAGAAGATCC
GGACCTCCGT TGGGATTTGA TGGACGACTG GTTGGCCGCC GTCTTCTAGG

13801 CCTCGTTGCA CAGTTTAAAC AGCGAGGAGG AGCGCATTTT GCGCTACGTG
GGAGCAACGT GTCAAATTTG TCGCTCCTCC TCGCGTAAAA CGCGATGCAC

13851 CAGCAGAGCG TGAGCCTTAA CCTGATGCGC GACGGGGTAA CGCCAGCGT
GTCGTCTCGC ACTCGGAATT GGACTACGCG CTGCCCCATT GCGGGTGCAG

13901 GGCCTGGAC ATGACCGCGC GCAACATGGA ACCGGGCATG TATGCCTCAA
CCGCGACCTG TACTGGCGCG CGTTGTACCT TGGCCCGTAC ATACGGAGTT

13951 ACCGGCCGTT TATCAACCGC CTAATGGACT ACTTGACATG CGCGGCCGCC
TGGCCGGCAA ATAGTTGGCG GATTACCTGA TGAACGTAGC GCGCCGGCGG

14001 GTGAACCCCG AGTATTTAC CAATGCCATC TTGAACCCCG ACTGGCTACC
CACTTGGGGC TCATAAAGTG GTTACGGTAG AACTTGGGCG TGACCGATGG

14051 GCCCCCTGGT TTCTACACCG GGGGATTCTGA GGTGCCCCGAG GGTAACGATG
CGGGGGACCA AAGATGTGGC CCCCTAAGCT CCACGGGCTC CCATTGCTAC

14101 GATTCTCTG GGACGACATA GACGACAGCG TGTTTTCCCC GCAACCGCAG
CTAAGGAGAC CCTGCTGTAT CTGCTGTGCG ACAAAGGGG CGTTGGCGTC

14151 ACCCTGCTAG AGTTGCAACA GCGCGAGCAG GCAGAGGCGG CGCTGCGAAA
TGGGACGATC TCAACGTTGT CGCGCTCGTC CGTCTCCGCC GCGACGCTTT

Figure 260

14251 CGCGGTCAGA TGCTAGTAGC CCATTTCCAA GCTTGATAGG GTCTCTTACC
GCGCCAGTCT ACGATCATCG GGTAAAGGTT CGAACTATCC CAGAGAATGG

14301 AGCACTCGCA CCACCCGCCC GCGCCTGCTG GGCAGGAGG AGTACCTAAA
TCGTGAGCGT GGTGGGCGGG CGCGGACGAC CCGCTCCTCC TCATGGATTT

14351 CAACTCGCTG CTGCAGCCGC AGCGCGAAAA AAACCTGCCT CCGGCATTTT
GTTGAGCGAC GACGTCGGCG TCGCGCTTTT TTTGGACGGA GGCCGTAAAG

14401 CCAACAACGG GATAGAGAGC CTAGTGAGCA AGATGAGTAG ATGGAAGACG
GGTTGTTGCC CTATCTCTCG GATCACCTGT TCTACTCATC TACCTTCTGC

14451 TACGCGCAGG AGCACAGGGA CGTGCCAGGC CCGCGCCCGC CCACCCGTCT
ATGCGCGTCC TCGTGTCCTT GCACGGTCCG GGCAGGGGCG GGTGGGCAGC

14501 TCAAAGGCAC GACCGTCAGC GGGGTCTGGT GTGGGAGGAC GATGACTCGG
AGTTTCCGTG CTGGCAGTCG CCCCAGACCA CACCCTCCTG CTACTGAGCC

14551 CAGACGACAG CAGCGTCCTG GATTTGGGAG GGAGTGGCAA CCCGTTTGCG
GTCTGTCTGTC GTCGCAGGAC CTAAACCCTC CCTCACCATT GGGCAAACGC

14601 CACCTTCGCC CCAGGCTGGG GAGAATGTTT TAAAAAATAA AAAAGCATGA
GTGGAAGCGG GGTCCGACCC CTCTTACAAA ATTTTTTTTT TTTTCGTACT

14651 TGCAAAATAA AAAACTCACC AAGGCCATGG CACCGAGCGT TGGTTTTCTT
ACGTTTTTATT TTTTGAGTGG TTCCGGTACC GTGGCTCGCA ACCAAAAGAA

14701 GTATTCCCCT TAGTATGCGG CGCGCGGCGA TGTATGAGGA AGGTCTCTCT
CATAAGGGGA ATCATACGCC GCGCGCCGCT ACATACTCCT TCCAGGAGGA

14751 CCCTCCTACG AGAGTGTGGT GAGCGCGGCG CCAGTGGCGG CGGCGCTGGG
GGGAGGATGC TCTCACACCA CTCGCGCCGC GGTCACCGCC GCCGCGACCC

14801 TTCTCCCTTC GATGCTCCCC TGGACCCGCC GTTTGTGCCT CCGCGGTACC
AAGAGGGAAG CTACGAGGGG ACCTGGGCGG CAAACACGGA GGCGCCATGG

14851 TGCGGCCTAC CGGGGGGAGA AACAGCATCC GTTACTCTGA GTTGGCACCC
ACGCCGGATG GCCCCCTCT TTGTCGTAGG CAATGAGACT CAACCGTGGG

14901 CTATTTCGACA CCACCCGTGT GTACCTGGTG GACAACAAGT CAACGGATGT
GATAAGCTGT GGTGGGCACA CATGGACCAC CTGTTGTTCA GTTGCCATA

14951 GGCATCCCTG AACTACCAGA ACGACCACAG CAACTTTCTG ACCACGGTCA
CCGTAGGGAC TTGATGGTCT TGCTGGTGTC GTTGAAAGAC TGGTGCCAGT

15001 TTCAAAACAA TGACTACAGC CCGGGGGAGG CAAGCACACA GACCATCAAT
AAGTTTGTGT ACTGATGTCT GGGCCCCCTC GTTCGTGTGT CTGGTAGTTA

15051 CTTGACGACC GGTGCACTG GGGCGGCGAC CTGAAAACCA TCCTGCATAC
GAACTGCTGG CCAGCGTGAC CCGCCGCTG GACTTTTGGT AGGACGTATG

15101 CAACATGCCA AATGTGAACG AGTTCATGTT TACCAATAAG TTTAAGGCGC
GTTGTACGGT TTACACTTGC TCAAGTACAA ATGGTTATTC AAATTCCGCG

Figure 26 P

15151 GGGTGA...GT GTCGCGCTTG CCTACTAAGG ACAATC...GT GGAGCTGAAA
 CCCACTACCA CAGCGCGAAC GGATGATTCC TGTTAGTCCA CCTCGACTTT

15201 TACGAGTGGG TGGAGTTCAC GCTGCCCCGAG GGCAACTACT CCGAGACCAT
 ATGCTCACCC ACCTCAAGTG CGACGGGCTC CCGTTGATGA GGCTCTGGTA

15251 GACCATAGAC CTTATGAACA ACGCGATCGT GGAGCACTAC TTGAAAGTGG
 CTGGTATCTG GAATACTTGT TGCCTAGCA CCTCGTGATG AACTTTCACC

15301 GCAGACAGAA CGGGGTCTTG GAAAGCGACA TCGGGGTAAA GTTTGACACC
 CGTCTGTCTT GCCCCAAGAC CTTTCGCTGT AGCCCCATTT CAAACTGTGG

15351 CGCAACTTCA GACTGGGGTT TGACCCCGTC ACTGGTCTTG TCATGCCTGG
 GCGTTGAAGT CTGACCCCAA ACTGGGGCAG TGACCAGAAC AGTACGGACC

15401 GGTATATACA AACGAAGCCT TCCATCCAGA CATCATTTTG CTGCCAGGAT
 CCATATATGT TTGCTTCGGA AGGTAGGTCT GTAGTAAAC GACGGTCTTA

15451 GCGGGGTGGA CTTACCCAC AGCCGCCTGA GCAACTTGTT GGGCATCCGC
 CGCCCCACCT GAAGTGGGTG TCGGCGGACT CGTTGAACAA CCCGTAGGCG

15501 AAGCGGCAAC CCTTCCAGGA GGGCTTTAGG ATCACCTACG ATGATCTGGA
 TTCGCCGTG GGAAGGTCTT CCCGAAATCC TAGTGGATGC TACTAGACCT

15551 GGGTGGTAAC ATTCCCGCAC TGTGGATGT GGACGCCTAC CAGGCGAGCT
 CCCACCATTG TAAGGGCGTG ACAACCTACA CCTGCGGATG GTCCGCTCGA

15601 TGAAAGATGA CACCGAACAG GGCGGGGGTG GCGCAGGCGG CAGCAACAGC
 ACTTTCTACT GTGGCTTGTC CCGCCCCAC CGCGTCCGCC GTCGTTGTGC

15651 AGTGGCAGCG GCGCGGAAGA GAACTCCAAC GCGGCAGCCG CGGCAATGCA
 TCACCGTCGC CGCGCCTTCT CTTGAGGTTG CGCCGTCGGC GCCGTTACGT

15701 GCCGGTGGAG GACATGAACG ATCATGCCAT TCGCGGCGAC ACCTTTGCCA
 CGGCCACCTC CTGTACTTGC TAGTACGGTA AGCGCCGCTG TGGAAACGGT

15751 CACGGGCTGA GGAGAAGCGC GCTGAGGCCG AAGCAGCGGC CGAAGCTGCC
 GTGCCCCACT CCTCTTCGCG CGACTCCGGC TTCGTCGCCG GCTTCGACGG

15801 GCCCCCGCTG CGCAACCCGA GGTGAGAGAAG CCTCAGAAGA AACC GGTTGAT
 CGGGGGCGAC GCGTTGGGCT CCAGCTCTTC GGAGTCTTCT TTGGCCACTA

15851 CAAACCCCTG ACAGAGGACA GCAAGAAACG CAGTTACAAC CTAATAAGCA
 GTTTGGGGAC TGTCTCCTGT CGTTCTTTGC GTCAATGTTG GATTATTCGT

15901 ATGACAGCAC CTTACCCAG TACCGCAGCT GGTACCTTGC ATACAACCTAC
 TACTGTCTGT GAAGTGGGTC ATGGCGTCGA CCATGGAACG TATGTTGATG

15951 GGCGACCCCTC AGACCGGAAT CCGCTCATGG ACCCTGCTTT GCACTCCTGA
 CCGCTGGGAG TCTGGCCTTA GGCGAGTACC TGGGACGAAA CGTGAGGACT

16001 CGTAACCTGC GGCTCGGAGC AGGTCTACTG GTCGTTGCCA GACATGATGC
 GCATTGGACG CCGAGCCTCG TCCAGATGAC CAGCAACGGT CTGTACTACG

16051 AAGACCCCGT GACCTTCCGC TCCACGCGCC AGATCAGCAA CTTTCCGGTG
 TTCTGGGGCA CTGGAAGGCG AGGTGCGCGG TCTAGTCGTT GAAAGGCCAC

Figure 26 A

16151 GGCCGTCTAC TCCCAACTCA TCCGCCAGTT TACCTCTCTG ACCCACGTGT
CCGGCAGATG AGGGTTGAGT AGGCGGTCAA ATGGAGAGAC TGGGTGCACA

16201 TCAATCGCTT TCCCGAGAAC CAGATTTTGG CGCGCCCGCC AGCCCCCACC
AGTTAGCGAA AGGGCTCTTG GTCTAAAACC GCGCGGGCGG TCGGGGGTGG

16251 ATCACCACCG TCAGTGAAAA CGTTCCTGCT CTCACAGATC ACGGGACGCT
TAGTGGTGGC AGTCACTTTT GCAAGGACGA GAGTGTCTAG TGCCCTGCGA

16301 ACCGCTGCGC AACAGCATCG GAGGAGTCCA GCGAGTGACC ATTACTGACG
TGGCGACGCG TTGTCGTAGC CTCTCAGGT CGCTCACTGG TAATGACTGC

16351 CCAGACGCCG CACCTGCCCC TACGTTTACA AGGCCCTGGG CATAGTCTCG
GGTCTGCGGC GTGGACGGGG ATGCAAAATGT TCCGGGACCC GTATCAGAGC

16401 CCGCGCGTCC TATCGAGCCG CACTTTTTGA GCAAGCATGT CCATCCTTAT
GGCGCGCAGG ATAGCTCGGC GTGAAAAACT CGTTCGTACA GGTAGGAATA

16451 ATCGCCCAGC AATAACACAG GCTGGGGCCT GCGCTTCCCA AGCAAGATGT
TAGCGGGTCG TTATTGTGTC CGACCCCGGA CGCGAAGGGT TCGTTCTACA

16501 TTGGCGGGGC CAAGAAGCGC TCCGACCAAC ACCCAGTGCG CGTGCGCGGG
AACCGCCCCG GTTCTTCGCG AGGCTGGTTG TGGGTCACGC GCACGCGCCC

16551 CACTACCGCG CGCCCTGGGG CGCGCACAAA CGCGGCCGCA CTGGGCGCAC
GTGATGGCGC GCGGGACCCC GCGCGTGTTT GCGCCGGCGT GACCCGCGTG

16601 CACCGTCGAT GACGCCATCG ACGCGGTGGT GGAGGAGGCG CGCAACTACA
GTGGCAGCTA CTGCGGTAGC TGCGCCACCA CCTCCTCCGC GCGTTGATGT

16651 CGCCACGCC GCCACCAGTG TCCACAGTGG ACGCGGCCAT TCAGACCGTG
GCGGGTGCGG CGGTGGTCAC AGGTGTCACC TGCGCCGTA AGTCTGGCAC

16701 GTGCGCGGAG CCCGGCGCTA TGCTAAAATG AAGAGACGGC GGAGGCGCGT
CACGCGCCTC GGGCCGCGAT ACGATTTTAC TTCTCTGCCG CCTCCGCGCA

16751 AGCACGTGCG CACCGCCGCC GACCCGGCAC TGCCGCCCAA CGCGCGGCGG
TCGTGCAGCG GTGGCGGCGG CTGGGCGGTG ACGGCGGGTT GCGCGCCCGC

16801 CGGCCCTGCT TAACCGCGCA CGTCGCACCG GCCGACGGGC GGCCATGCGG
GCCGGGACGA ATTGGCGCGT GCAGCGTGGC CGGCTGCCCC CCGGTACGCC

16851 GCCGCTCGAA GGCTGGCCGC GGGTATTGTC ACTGTGCCCC CCAGGTCCAG
CGGCGAGCTT CCGACCGGCG CCCATAACAG TGACACGGGG GGTCCAGGTC

16901 GCGACGAGCG GCCGCCGCG CAGCCGCGGC CATTAGTGCT ATGACTCAGG
CGCTGCTCGC CGGCGGCGTC GTCGGCGCCG GTAATCACGA TACTGAGTCC

16951 GTCGCAGGGG CAACGTGTAT TGGGTGCGCG ACTCGGTTAG CGGCCTGCGC
CAGCGTCCCC GTTGACATA ACCCACGCGC TGAGCCAATC GCCGGACGCG

17001 GTGCCCCGTGC GCACCCGCCC CCCGCGCAAC TAGATTGCAA GAAAAAATA
CACGGGCACG CGTGGGCGGG GGGCGCGTTG ATCTAACGTT CTTTTTTGAT

Figure 26 R

17101	CTATGTCCAA GATACAGGTT	GCGCAAAATC CGCGTTTTAG	AAAGAAGAGA TTTCTTCTCT	TGCTCCAGGT ACGAGGTCCA	CATCGCGCCC GTAGCGCGGC
17151	GAGATCTATG CTCTAGATAC	GCCCCCGAA CGGGGGGCTT	GAAGGAAGAG CTTCCTTCTC	CAGGATTACA GTCCTAATGT	AGCCCCGAAA TCGGGGCTTT
17201	GCTAAAGCGG CGATTTTCGCC	GTCAAAAAGA CAGTTTTTCT	AAAAGAAAGA TTTTCTTTCT	TGATGATGAT ACTACTACTA	GAAGTTGACG CTTGAAGTGC
17251	ACGAGGTGGA TGCTCCACCT	ACTGCTGCAC TGACGACGTG	GCTACCGCGC CGATGGCGCG	CCAGGCGACG GGTCCGCTGC	GGTACAGTGG CCATGTCACC
17301	AAAGGTGCAC TTTCCAGCTG	GCGTAAAACG CGCATTTTGC	TGTTTTGCGA ACAAAACGCT	CCCGGCACCA GGGCCGTGGT	CCGTAGTCTT GGCATCAGAA
17351	TACGCCCCGT ATGCGGGCCA	GAGCGCTCCA CTCGCGAGGT	CCCGCACCTA GGGCGTGGAT	CAAGCGCGTG GTTGCGGCAC	TATGATGAGG ATACTACTCC
17401	TGTACGGCGA ACATGCCGCT	CGAGGACCTG GCTCCTGGAC	CTTGAGCAGG GAATCGTCC	CCAACGAGCG GGTTGCTCGC	CCTCGGGGAG GGAGCCCCTC
17451	TTTGCCTACG AAACGGATGC	GAAAGCGGCA CTTTCGCCGT	TAAGGACATG ATTCTGTAC	CTGGCGTTGC GACCGCAACG	CGCTGGACGA GCGACCTGCT
17501	GGGCAACCCA CCCGTTGGGT	ACACCTAGCC TGTGGATCGG	TAAAGCCCGT ATTTCCGGCA	AACACTGCAG TTGTGACGTC	CAGGTGCTGC GTCCACGACG
17551	CCGCGCTTGC GGCGCGAACG	ACCGTCCGAA TGGCAGGCTT	GAAAAGCGCG CTTTTCGCGC	GCCTAAAGCG CGGATTTTCG	CGAGTCTGGT GCTCAGACCA
17601	GACTTGGCAC CTGAACCGTG	CCACCGTGCA GGTGGCACGT	GCTGATGGTA CGACTACCAT	CCCAAGCGCC GGGTTCGCGG	AGCGACTGGA TCGCTGACCT
17651	AGATGTCTTG TCTACAGAAC	GAAAAAATGA CTTTTTTACT	CCGTGGAACC GGCACCTTGG	TGGGCTGGAG ACCCGACCTC	CCCAGGTGCC GGGCTCCAGG
17701	GCGTGCGGCC CGCACGCCGG	AATCAAGCAG TTAGTTCGTC	GTGGCGCCGG CACCGCGGCC	GACTGGGCGT CTGACCCGCA	GCAGACCGTG CGTCTGGCAC
17751	GACGTTTCTG CTGCAAGTCT	TACCCACTAC ATGGGTGATG	CAGTAGCACC GTCATCGTGG	AGTATTGCCA TCATAACGGT	CCGCCACAGA GGCGGTGTCT
17801	GGGCATGGAG CCCGTACCTC	ACACAAACGT TGTGTTTGCA	CCCCGGTTGC GGGGCCAACG	CTCAGCGGTG GAGTCGCCAC	GCGGATGCCG CGCCTACGGC
17851	CGGTGCAGGC GCCACGTCCG	GGTCGCTGCG CCAGCGACGC	GCCGCGTCCA CGGCGCAGGT	AGACCTCTAC TCTGGAGATG	GGAGGTGCAA CCTCCACGTT
17901	ACGGACCCGT TGCTTGCGCA	GGATGTTTTG CCTACAAAGC	CGTTTCAGCC GCAAAGTCGG	CCCCGGCGCC GGGGCCGCGG	CGCGCCGTTC GCGCGGCAAG
17951	GAGGAAGTAC CTCCTTCATG	GGCGCCGCCA CCGCGGCGGT	GCGCGCTACT CGCGCGATGA	GCCCCAATAT CGGGCTTATA	GCCCTACATC CGGGATGTAG

Figure 26S

18051 AGACGAGCAA CTACCCGACG CCGAACCACC ACTGGAACCC GCCGCCGCCG
TCTGCTCGTT GATGGGCTGC GGCTTGGTGG TGACCTTGGG CGGCGGCGGC

18101 TCGCCGTGCG CAGCCCGTGC TGGCCCCGAT TTCCGTGCGC AGGGTGGCTC
AGCGGCAGCG GTCGGGCACG ACCGGGGCTA AAGGCACGCG TCCCACCGAG

18151 GCGAAGGAGG CAGGACCCTG GTGCTGCCAA CAGCGCGCTA CCACCCACGC
CGCTTCCTCC GTCCTGGGAC CACGACGGTT GTCGCGCGAT GGTGGGGTGC

18201 ATCGTTTAAA AGCCGGTCTT TGTGGTTCTT GCAGATATGG CCCTCACCTG
TAGCAAATTT TCGGCCAGAA ACACCAAGAA CGTCTATACC GGGAGTGGAC

18251 CCGCCTCCGT TTCCCGGTGC CGGGATTCCG AGGAAGAATG CACCGTAGGA
GGCGGAGGCA AAGGGCCACG GCCCTAAGGC TCCTTCTTAC GTGGCATCCT

18301 GGGGCATGGC CGGCCACGGC CTGACGGGCG GCATGCGTCG TGCGCACCAC
CCCCGTACCG GCCGGTGCCG GACTGCCCGC CGTACGCAGC ACGCGTGGTG

18351 CGGCGGCGGC GCGCGTCGCA CCGTCGCATG CGCGGCGGTA TCCTGCCCCCT
GCCGCCGCCG CGCGCAGCGT GGCAGCGTAC GCGCCGCCAT AGGACGGGGA

18401 CCTTATTCCA CTGATCGCCG CGGCGATTGG CGCCGTGCCC GGAATTGCAT
GGAATAAGGT GACTAGCGGC GCCGCTAACC GCGGCACGGG CCTTAACGTA

18451 CCGTGGCCTT GCAGGCGCAG AGACACTGAT TAAAAACAAG TTGCATGTGG
GGCACCGGAA CGTCCGCGTC TCTGTGACTA ATTTTGTTC AACGTACACC

18501 AAAAATCAAA ATAAAAAGTC TGGACTCTCA CGCTCGCTTG GTCCTGTAAC
TTTTTAGTTT TATTTTTCAG ACCTGAGAGT GCGAGCGAAC CAGGACATTG

18551 TATTITGTAG AATGGAAGAC ATCAACTTTG CGTCTCTGGC CCCGCGACAC
ATAAAACATC TTACCTTCTG TAGTTGAAAC GCAGAGACCG GGGCGCTGTG

18601 GGCTCGCGCC CGTTCATGGG AAACCTGGCAA GATATCGGCA CCAGCAATAT
CCGAGCGCGG GCAAGTACCC TTTGACCGTT CTATAGCCGT GGTCGTTATA

18651 GAGCGGTGGC GCCTTCAGCT GGGGCTCGCT GTGGAGCGGC ATTAAAAATT
CTCGCCACCG CGGAAGTCGA CCCCAGCGCA CACCTCGCCG TAATTTTAA

18701 TCGGTTCCAC CGTTAAGAAC TATGGCAGCA AGGCCTGGAA CAGCAGCACA
AGCCAAGGTG GCAATTCTTG ATACCGTCGT TCCGGACCTT GTCGTCGTGT

18751 GGCCAGATGC TGAGGGATAA GTTGAAAGAG CAAAATTTCC AACAAAAGGT
CCGGTCTACG ACTCCCTATT CAACCTTCTC GTTTTAAAGG TTGTTTCCA

18801 GGTAGATGGC CTGGCCTCTG GCATTAGCGG GGTGGTGGAC CTGGCCAACC
CCATCTACCG GACCGGAGAC CGTAATCGCC CCACCACCTG GACCGGTG

18851 AGGCAGTGCA AAATAAGATT AACAGTAAGC TTGATCCCCG CCCTCCCGTA
TCCGTCACGT TTTATTCTAA TTGTCATTG AACTAGGGGC GGGAGGGCAT

18901 GAGGAGCCTC CACCGGCCGT GGAGACAGTG TCTCCAGAGG GCGGTGGCGA
CTCCTCGGAG GTGGCCGGCA CCTCTGTCAC AGAGGTCTCC CCGCACCGCT

Figure 26.T

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19001  AGCCTCCCTC GTACGAGGAG GCACTAAAGC AAGGCCTGCC CACCACCCGT
        TCGGAGGGAG CATGCTCCTC CGTGATTTCG TTCCGGACGG GTGGTGGGCA

19051  CCCATCGCGC CCATGGCTAC CGGAGTGCTG GGCCAGCACA CACCCGTAAC
        GGGTAGCGCG GGTACCGATG GCCTCACGAC CCGGTCGTGT GTGGGCATTG

19101  GCTGGACCTG CCTCCCCCG CCGACACCCA GCAGAAACCT GTGCTGCCAG
        CGACCTGGAC GGAGGGGGGC GGCTGTGGGT CGTCTTTGGA CACGACGGTC

19151  GCCCGACCGC CGTTGTTGTA ACCCGTCCTA GCCGCGCGTC CCTGCGCCGC
        CGGGCTGGCG GCAACAACAT TGGGCAGGAT CGGCGCGCAG GGACGCGGCG

19201  GCCGCCAGCG GTCCGCGATC GTTGCGGGCC GTAGCCAGTG GCAACTGGCA
        CGGCGGTCGC CAGGCGCTAG CAACGCCGGG CATCGGTCAC CGTTGACCGT

19251  AAGCACACTG AACAGCATCG TGGGTCTGGG GGTGCAATCC CTGAAGCGCC
        TTCGTGTGAC TTGTCGTAGC ACCCAGACCC CCACGTTAGG GACTTCGCGG

19301  GACGATGCTT CTGATAGCTA ACGTGTGCTA TGTGTGTCAT GTATGCGTCC
        CTGCTACGAA GACTATCGAT TGCACAGCAT ACACACAGTA CATACGCAGG

19351  ATGTCGCCGC CAGAGGAGCT GCTGAGCCGC CGCGCGCCCG CTTTCCAAGA
        TACAGCGGCG GTCTCCTCGA CGACTCGGCG GCGCGCGGGC GAAAGGTTCT

19401  TGGCTACCCC TTCGATGATG CCGCAGTGGT CTTACATGCA CATCTCGGGC
        ACCGATGGGG AAGCTACTAC GGCCTACCA GAATGTACGT GTAGAGCCCG

19451  CAGGACGCCT CGGAGTACCT GAGCCCCGGG CTGGTGCACT TTGCCCCGCGC
        GTCTTGCAGA GCCTCATGGA CTCGGGGCCC GACCACGTCA AACGGGCGCG

19501  CACCGAGACG TACTTCAGCC TGAATAACAA GTTTAGAAAC CCCACGGTGG
        GTGGCTCTGC ATGAAGTCGG ACTTATTGTT CAAATCTTTG GGGTGCCACC

19551  CGCCTACGCA CGACGTGACC ACAGACCGGT CCCAGCGTTT GACGCTGCGG
        GCGGATGCGT GCTGCACTGG TGTCTGGCCA GGGTCGCAA CTGCGACGCC

19601  TTCATCCCTG TGGACCGTGA GGATACTGCG TACTCGTACA AGGCGCGGTT
        AAGTAGGGAC ACCTGGCACT CCTATGACGC ATGAGCATGT TCCGCGCCAA

19651  CACCCTAGCT GTGGGTGATA ACCGTGTGCT GGACATGGCT TCCACGTACT
        GTGGGATCGA CACCCACTAT TGGCACACGA CCTGTACCGA AGGTGCATGA

19701  TTGACATCCG CGGCGTGCTG GACAGGGGCC CTACTTTTAA GCCCTACTCT
        AACTGTAGGC GCCGCACGAC CTGTCCCCGG GATGAAAATT CGGGATGAGA

19751  GGCCTGCGCT ACAACGCCCT GGCTCCCAAG GGTGCCCCAA ATCCTTGCGA
        CCGTGACGGA TGTTGCGGGA CCGAGGGTTC CCACGGGGTT TAGGAACGCT

19801  ATGGGATGAA GCTGCTACTG CTCTTGAAAT AAACCTAGAA GAAGAGGACG
        TACCCTACTT CGACGATGAC GAGAACTTTA TTTGGATCTT CTTCTCCTGC

19851  ATGACAACGA AGACGAAGTA GACGAGCAAG CTGAGCAGCA AAAAACTCAC
        TACTGTTGCT TCTGCTTCAT CTGCTCGTTC GACTCGTCGT TTTTGTAGTG

```

Figure 26 u

19951 TCAAATAGGT GTCGAAGGTC AAACACCTAA ATATGCCGAT AAAACATTTT
 AGTTTATCCA CAGCTTCCAG TTTGTGGATT TATACGGCTA TTTTGTAAAG
 20001 AACCTGAACC TCAAATAGGA GAATCTCAGT GGTACGAAAC AGAAATTAAT
 TTGGACTTGG AGTTTATCCT CTTAGAGTCA CCATGCTTTG TCTTTAATTA
 20051 CATGCAGCTG GGAGAGTCCT AAAAAAGACT ACCCCAATGA AACCATGTTA
 GTACGTCGAC CCTCTCAGGA TTTTTTCTGA TGGGGTTACT TTGGTACAAT
 20101 CGGTTTCATAT GCAAAACCCA CAAATGAAAA TGGAGGGCAA GGCATTCTTG
 GCCAAGTATA CGTTTTGGGT GTTTACTTTT ACCTCCCGTT CCGTA-GAAC
 20151 TAAAGCAACA AAATGGAAAG CTAGAAAGTC AAGTGGAAAT GCAATTTTTC
 ATTCGTTGT TTTACCTTTC GATCTTTCAG TTCACCTTTA CGTTAAAAAG
 20201 TCAACTACTG AGGCAGCCGC AGGCAATGGT GATAACTTGA CTCCTAAAGT
 AGTTGATGAC TCCGTCGGCG TCCGTTACCA CTATTGAACT GAGGATTTCA
 20251 GGTATTGTAC AGTGAAGATG TAGATATAGA AACCCCAGAC ACTCATATTT
 CCATAACATG TCACTTCTAC ATCTATATCT TTGGGGTCTG TGAGTATAAA
 20301 CTTACATGCC CACTATTAAG GAAGGTAAC CACGAGAACT AATGGGCCAA
 GAATGTACGG GTGATAATTC CTTCCATTGA GTGCTCTTGA TTACCCGGTT
 20351 CAATCTATGC CCAACAGGCC TAATTACATT GCTTTTAGGG ACAATTTTAT
 GTTAGATACG GGTGTGCCG ATTAATGTAA CGAAATCCC TGTTAAAATA
 20401 TGGTCTAATG TATTACAACA GCACGGGTAA TATGGGTGTT CTGGCGGGCC
 ACCAGATTAC ATAATGTTGT CGTGCCCATT ATACCCACAA GACCGCCCGG
 20451 AAGCATCGCA GTTGAATGCT GTTGTAGATT TGCAAGACAG AAACACAGAG
 TTCGTAGCGT CAACTTACGA CAACATCTAA ACGTTCTGTC TTTGTGTCTC
 20501 CTTTCATACC AGCTTTTGCT TGATTCCATT GGTGATAGAA CCAGGTACTT
 GAAAGTATGG TCGAAAACGA ACTAAGGTAA CCACTATCTT GGTCCATGAA
 20551 TTCTATGTGG AATCAGGCTG TTGACAGCTA TGATCCAGAT GTTAGAATTA
 AAGATACACC TTAGTCCGAC AACTGTGCGAT ACTAGGTCTA CAATCTTAAT
 20601 TTGAAAATCA TGGAACTGAA GATGAACTTC CAAATTACTG CTTTCCACTG
 AACTTTTAGT ACCTTGACTT CTACTTGAAG GTTTAATGAC GAAAGGTGAC
 20651 GGAGGTGTGA TTAATACAGA GACTCTTACC AAGGTAAAAC CTAAAACAGG
 CCTCCACACT AATTATGTCT CTGAGAAATG TTCCATTTTG GATTTTGTCC
 20701 TCAGGAAAAT GGATGGGAAA AAGATGCTAC AGAATTTTCA GATAAAAATG
 AGTCCTTTTA CCTACCCCTT TTCTACGATG TCTTAAAAGT CTATTTTAC
 20751 AAATAAGAGT TGGAAATAAT TTTGCCATGG AAATCAATCT AAATGCCAAC
 TTTATTCTCA ACCTTTATTA AAACGGTACC TTTAGTTAGA TTTACGGTTG
 20801 CTGTGGAGAA ATTTCCCTGA CTCCAACATA GCGCTGTATT TGCCCGACAA
 GACACCTCTT TAAAGGACAT GAGGTTGTAT CGCGACATAA ACGGGCTGTT

Figure 26 v

20901 ACGACTACAT GAACAAGCGA GTGGTGGCTC CCGGGCTAGT GGA CTGCTAC
TGCTGATGTA CTTGTTGCT CACCACCGAG GGCCCGATCA CCTGACGATG

20951 ATTAACCTTG GAGCACGCTG GTCCCTTGAC TATATGGACA ACGTCAACCC
TAATTGGAAC CTCGTGCGAC CAGGGAAGTG ATATACCTGT TGCAGTTGGG

21001 ATTTAACCAC CACCGCAATG CTGGCCTGCG CTACCGCTCA ATGTTGCTGG
TAAATTGGTG GTGGCGTTAC GACCGGACGC GATGGCGAGT TACAACGACC

21051 GCAATGGTCTG CTATGTGCCC TTCCACATCC AGGTGCCTCA GAAGTTCTTT
CGTTACCAGC GATACACGGG AAGGTGTAGG TCCACGGAGT CTTCAAGAAA

21101 GCCATTAAAA ACCTCCTTCT CCTGCCGGGC TCATACACCT ACGAGTGGAA
CGGTAATTTT TGGAGGAAGA GGACGGCCCG AGTATGTGGA TGCTCACCTT

21151 CTTCAGGAAG GATGTTAACA TGGTTCTGCA GAGCTCCCTA GGAAATGACC
GAAGTCCTTC CTACAATTGT ACCAAGACGT CTCGAGGGAT CCTTTACTGG

21201 TAAGGGTTGA CGGAGCCAGC ATTAAGTTTG ATAGCATTTG CCTTTACGCC
ATTCCCAACT GCCTCGGTCTG TAATTCAAAC TATCGTAAAC GGAAATGCGG

21251 ACCTTCTTCC CCATGGCCCA CAACACCGCC TCCACGCTTG AGGCCATGCT
TGGAAGAAGG GGTACCGGGT GTTGTGGCGG AGGTGCGAAC TCCGGTACGA

21301 TAGAAACGAC ACCAACGACC AGTCCTTTAA CGACTATCTC TCCGCCGCCA
ATCTTTGCTG TGGTTGCTGG TCAGGAAATT GCTGATAGAG AGGCGGCGGT

21351 ACATGCTCTA CCCTATACCC GCCAACGCTA CCAACGTGCC CATATCCATC
TGTACGAGAT GGGATATGGG CGGTTGCGAT GGTTCACGG GTATAGGTAG

21401 CCCTCCCGCA ACTGGGCGGC TTTCCGCGGC TGGGCCTTCA CGCGCCTTAA
GGGAGGGCGT TGACCCGCCG AAAGGCGCCG ACCCGGAAGT GCGCGGAATT

21451 GACTAAGGAA ACCCCATCAC TGGGCTCGGG CTACGACCCT TATTACACCT
CTGATTCCTT TGGGGTAGTG ACCCGAGCCC GATGCTGGGA ATAATGTGGA

21501 ACTCTGGCTC TATACCCTAC CTAGATGGAA CCTTTTACCT CAACCACACC
TGAGACCGAG ATATGGGATG GATCTACCTT GGAAAATGGA GTTGGTGTGG

21551 TTTAAGAAGG TGGCCATTAC CTTTGACTCT TCTGTCAGCT GGCCTGGCAA
AAATTCTTCC ACCGGTAATG GAAACTGAGA AGACAGTCGA CCGGACCGTT

21601 TGACCGCCTG CTTACCCCCA ACGAGTTTGA AATTAAGCGC TCAGTTGACG
ACTGGCGGAC GAATGGGGGT TGCTCAAAC TTAATTCGCG AGTCAACTGC

21651 GGGAGGGTTA CAACGTTGCC CAGTGTAACA TGACCAAAGA CTGGTTCTCTG
CCCTCCCAAT GTTGCAACGG GTCACATTGT ACTGGTTTCT GACCAAGGAC

21701 GTACAAATGC TAGCTAACTA TAACATTGGC TACCAGGGCT TCTATATCCC
CATGTTTACG ATCGATTGAT ATTGTAACCG ATGGTCCCGA AGATATAGGG

21751 AGAGAGCTAC AAGGACCGCA TGTACTCCTT CTTTAGAAAC TTCCAGCCCA
TCTCTCGATG TTCCTGGCGT ACATGAGGAA GAAATCTTTG AAGGTCGGGT

Figure 26 W

21851 GGCATCCTAC ACCAACACAA CAACTCTGGA TTTGTTGGCT ACCTTGCCCC
CCGTAGGATG TGGTTGTGTT GTTGAGACCT AAACAACCGA TGGAACGGGG

21901 CACCATGCGC GAAGGACAGG CCTACCTGTC TAACTTCCCC TATCCGCTTA
GTGGTACGCG CTTCTGTCC GGATGGGACG ATTGAAGGGG ATAGGCGAAT

21951 TAGGCAAGAC CGCAGTTGAC AGCATTACCC AGAAAAAGTT TCTTTGCGAT
ATCCGTTCTG GCGTCAACTG TCGTAATGGG TCTTTTTCAA AGAAACGCTA

22001 CGCACCTTTT GGCGCATCCC ATTCTCCAGT AACTTTATGT CCATGGGCGC
GCGTGGGAAA CCGCGTAGGG TAAGAGGTCA TTGAAATACA GGTACCCGCG

22051 ACTCACAGAC CTGGGCCAAA ACCTTCTCTA CGCCAACTCC GCCCACGCGC
TGAGTGTCTG GACCCGGTTT TGGAAAGAGAT GCGGTTGAGG CGGGTGCGCG

22101 TAGACATGAC TTTTGAGGTG GATCCCATGG ACGAGCCCAC CCTTCTTTAT
ATCTGTACTG AAAACTCCAC CTAGGGTACC TGCTCGGGTG GGAAGAAATA

22151 GTTTTGTGTTG AAGTCTTTGA CGTGGTCCGT GTGCACCAGC CGCACCGCGG
CAAAACAAAC TTCAGAACT GCACCAGGCA CACGTGGTCG GCGTGGCGCC

22201 CGTCATCGAA ACCGTGTACC TGCGCACGCC CTTCTCGGCC GGCAACGCCA
GCAGTAGCTT TGGCACATGG ACGCGTGCGG GAAGAGCCGG CCGTTGCGGT

22251 CAACATAAAG AAGCAAGCAA CATCAACAAC AGCTGCCGCC ATGGGCTCCA
GTTGTATTTT TCGTTTCGTT GTAGTTGTTG TCGACGGCGG TACCCGAGGT

22301 GTGAGCAGGA ACTGAAAGCC ATTGTCAAAG ATCTTGGGTG TGGGCCATAT
CACTCGTCCT TGACTTTCGG TAACAGTTTC TAGAACCAAC ACCCGGTATA

22351 TTTTGGGCA CCTATGACAA GCGCTTTCCA GGCTTTGTTT CTCCACACAA
AAAAACCCGT GGATACTGTT CGCGAAAGGT CCGAAACAAA GAGGTGTGTT

22401 GCTCGCCTGC GCCATAGTCA ATACGGCCGG TCGCGAGACT GGGGGCGTAC
CGAGCGGACG CCGTATCAGT TATGCCGGCC AGCGCTCTGA CCCCCGATG

22451 ACTGGATGGC CTTTGCTGG AACC CGCACT CAAAAACATG CTACCTCTTT
TGACCTACCG GAAACGGACC TTGGGCGTGA GTTTTGTAC GATGGAGAAA

22501 GAGCCCTTTG GCTTTTCTGA CCAGCGACTC AAGCAGGTTT ACCAGTTTGA
CTCGGGAAAC CGAAAAGACT GGTGCTGAG TTCGTCCAA TGGTCAAAC

22551 GTACGAGTCA CTCCTGCGCC GTAGCGCCAT TGCTTCTTCC CCCGACCGCT
CATGCTCAGT GAGGACGCGG CATCGCGGTA ACGAAGAAGG GGGCTGGCGA

22601 GTATAACGCT GGAAAAGTCC ACCCAAAGCG TACAGGGGCC CAACTCGGCC
CATATTGCGA CCTTTTCAGG TGGGTTTCGC ATGTCCCCGG GTTGAGCCGG

22651 GCCTGTGGAC TATTCTGCTG CATGTTTCTC CACGCCTTTG CCAACTGGCC
CGGACACCTG ATAAGACGAC GTACAAAGAG GTGCGGAAAC GGTGACCCG

22701 CCAAACCTCC ATGGATCACA ACCCCACCAT GAACCTTATT ACCGGGGTAC
GGTTTGAGGG TACCTAGTGT TGGGGTGGTA CTTGGAATAA TGGCCCCATG

Figure 26 x

22801 CAGGAACAGC TCTACAGCTT CCTGGAGCGC CACTCGCCCT ACTTCGCGAG
GTCTTTGTCTG AGATGTCGAA GGACCTCGCG GTGAGCGGGA TGAAGGCGTC

22851 CCACAGTGCG CAGATTAGGA GCGCCACTTC TTTTGTGTCAC TTGAAAAACA
GGTGTACGCG GTCTAATCCT CGCGGTGAAG AAAAACAGTG AACTTTTTGT

22901 TGTA AAAATA ATGTACTAGA GACACTTTCA ATAAAGGCAA ATGCTTTTAT
ACATTTTAT TACATGATCT CTGTGAAAGT TATTTCCGTT TACGAAAATA

22951 TTGTACACTC TCGGGTGATT ATTTACCCCT ACCCTTGCCG TCTGCGCCGT
AACATGTGAG AGCCCACTAA TAAATGGGGG TGGGAACGGC AGACGCGGCA

23001 TTAAAAATCA AAGGGGTTCT GCCGCGCATC GCTATGCGCC ACTGGCAGGG
AATTTTATGT TTCCCAAGA CGGCGCGTAG CGATACGCGG TGACCGTCCC

23051 ACACGTTGCG ATACTGGTGT TTAGTGCTCC ACTTAACTC AGGCACAACC
TGTGCAACGC TATGACCACA AATCACGAGG TGAATTTGAG TCCGTGTTGG

23101 ATCCGCGGCA GCTCGGTGAA GTTTTCACTC CACAGGCTGC GCACCATCAC
TAGGCGCCGT CGAGCCACTT CAAAAGTGAG GTGTCCGACG CGTGGTAGTG

23151 CAACGCGTTT AGCAGGTCGG GCGCCGATAT CTTGAAGTCG CAGTTGGGGC
GTTGCGCAA TCGTCCAGCC CGCGGCTATA GAACTTCAGC GTCAACCCCG

23201 CTCCGCCCTG CGCGCGCGAG TTGCGATACA CAGGGTTGCA GCACTGGAAC
GAGGCGGGAC GCGCGCGCTC AACGCTATGT GTCCCAACGT CGTGACCTTG

23251 ACTATCAGCG CCGGGTGGTG CACGCTGGCC AGCACGCTCT TGTCGGAGAT
TGATAGTCGC GGCCACCAC GTGCGACCGG TCGTGCGAGA ACAGCCTCTA

23301 CAGATCCGCG TCCAGGTCCT CCGCGTTGCT CAGGGCGAAC GGAGTCAACT
GTCTAGGCGC AGGTCCAGGA GGCGCAACGA GTCCCGCTTG CCTCAGTTGA

23351 TTGGTAGCTG CCTTCCCAA AAGGGCGCGT GCCCAGGCTT TGAGTTGCAC
AACCATCGAC GGAAGGGTTT TTCCCGCGCA CGGGTCCGAA ACTCAACGTG

23401 TCGCACCGTA GTGGCATCAA AAGGTGACCG TGCCCGGTCT GGGCGTTAGG
AGCGTGGCAT CACCGTAGTT TTCCACTGGC ACGGGCCAGA CCCGCAATCC

23451 ATACAGCGCC TGCATAAAAG CCTTGATCTG CTTAAAAGCC ACCTGAGCCT
TATGTGCGCG ACGTATTTT GGAAC TAGAC GAATTTTCGG TGGACTCGGA

23501 TTGCGCCTTC AGAGAAGAAC ATGCCGCAAG ACTTGCCGGA AACTGATTG
AACGCGGAAG TCTCTTCTTG TACGGCGTTC TGAACGGCCT TTTGACTAAC

23551 GCCGGACAGG CCGCGTCGTG CACGCAGCAC CTTGCGTCGG TGTTGGAGAT
CGGCCTGTCC GCGCAGCAC GTGCGTCGTG GAACGCAGCC ACAACCTCTA

23601 CTGCACCACA TTTCGGCCCC ACCGGTTCTT CACGATCTTG GCCTTGCTAG
GACGTGGTGT AAAGCCGGGG TGGCCAAGAA GTGCTAGAAC CGGAACGATC

23651 ACTGCTCCTT CAGCGCGCGC TGCCCGTTTT CGCTCGTCAC ATCCATTTC
TGACGAGGAA GTCGCGCGCG ACGGGCAAAA GCGAGCAGTG TAGGTAAAGT

Figure 26Y

23701 ATCACGTGCT CTTATTTAT CATAATGCTT CCGTGTAGAC ACTTAAGCTC
TAGTGCACGA GGAATAAATA GTATTACGAA GGCACATCTG TGAATTTCAG

23751 GCCTTCGATC TCAGCGCAGC GGTGCAGCCA CAACGCGCAG CCCGTGGGCT
CGGAAGCTAG AGTCGCGTCG CCACGTCGGT GTTGCGCGTC GGGCACCCGA

23801 CGTGATGCTT GTAGGTCACC TCTGCAAACG ACTGCAGGTA CGCCTGCAGG
GCACTACGAA CATCCAGTGG AGACGTTTGC TGACGTCCAT GCGGACGTCC

23851 AATCGCCCCA TCATCGTCAC AAAGGTCTTG TTGCTGGTGA AGGTCAGCTG
TTAGCGGGGT AGTAGCAGTG TTTCCAGAAC AACGACCACT TCCAGTCGAC

23901 CAACCCGCGG TGCTCCTCGT TCAGCCAGGT CTTGCATACG GCCGCCAGAG
GTTGGGCGCC ACGAGGAGCA AGTCGGTCCA GAACGTATGC CGGCGGTCTC

23951 CTTCCACTTG GTCAGGCAGT AGTTTGAAGT TCGCCTTTAG ATCGTTATCC
GAAGGTGAAC CAGTCCGTCA TCAAACTTCA AGCGGAAATC TAGCAATAGG

24001 ACGTGGTACT TGTCCATCAG CGCGCGCGCA GCCTCCATGC CCTTCTCCCA
TGCACCATGA ACAGGTAGTC GCGCGCGCGT CGGAGGTACG GGAAGAGGGT

24051 CGCAGACACG ATCGGCACAC TCAGCGGGTT CATCACCGTA ATTTCACTTT
GCGTCTGTGC TAGCCGTGTG AGTCGCCCAA GTAGTGGCAT TAAAGTGAAA

24101 CCGCTTCGCT GGGCTCTTCC TCTTCTCTT GCGTCCGCAT ACCACGCGCC
GGCGAAGCGA CCCGAGAAGG AGAAGGAGAA CGCAGGCGTA TGGTGC GCGG

24151 ACTGGGTCGT CTTCAATCAG CCGCCGCACT GTGCGCTTAC CTCCTTTGCC
TGACCCAGCA GAAGTAAAGTC GCGGCGGTGA CACGCGAATG GAGGAAACGG

24201 ATGCTTGATT AGCACCGGTG GGTGCTGAA ACCCACCATT TGTAGCGCCA
TACGAATAA TCGTGGCCAC CCAACGACTT TGGGTGGTAA ACATCGCGGT

24251 CATCTTCTCT TTCTTCTCTG CTGTCCACGA TTACCTCTGG TGATGGCGGG
GTAGAAGAGA AAGAAGGAGC GACAGGTGCT AATGGAGACC ACTACCGCCC

24301 CGCTCGGGCT TGGGAGAAGG GCGCTTCTTT TTCTTCTTGG GCGCAATGGC
GCGAGCCCGA ACCCTCTTCC CGCGAAGAAA AAGAAGAACC CGCGTTACCG

24351 CAAATCCGCC GCCGAGGTG ATGGCCGCGG GCTGGGTGTG CGCGGCACCA
GTTTAGGCGG CGGCTCCAGC TACCGGCGCC CGACCCACAC GCGCCGTGGT

24401 GCGCGTCTTG TGATGAGTCT TCCTCGTCCT CGGACTCGAT ACGCCGCCTC
CGCGCAGAAC ACTACTCAGA AGGAGCAGGA GCCTGAGCTA TGCGGCGGAG

24451 ATCCGCTTTT TTGGGGGCGC CCGGGGAGGC GCGGCGGACG GGGACGGGGA
TAGGCGAAAA AACCCCCGCG GGGCCCTCCG CCGCCGCTGC CCCTGCCCCT

24501 CGACACGTCC TCCATGGTTG GGGGACGTG CGCCGCACCG CGTCCGCGCT
GCTGTGCAGG AGGTACCAAC CCCCTGCAGC GCGGCGTGGC GCAGGCGCGA

24551 CGGGGGTGGT TTCGCGCTGC TCCTCTTCCC GACTGGCCAT TTCCTTCTCC
GCCCCACCA AAGCGCGACG AGGAGAAGGG CTGACCGGTA AAGGAAGAGG

24601 TATAGGCAGA AAAAGATCAT GGAGTCAGTC GAGAAGAAGG ACAGCCTAAC
ATATCCGTCT TTTTCTAGTA CCTCAGTCAG CTCTTCTTCC TGTCGGATTG

24701 CTACCACCTT CCCCCTCGAG GCACCCCGC TTGAGGAGGA GGAAGTGATT
 GATGGTGGAA GGGGCAGCTC CGTGGGGGCG AACTCCTCCT CCTTCACTAA
 24751 ATCGAGCAGG ACCCAGGTTT TGTAAGCGAA GACGACGAGG ACCGCTCAGT
 TAGCTCGTCC TGGGTCCAAA ACATTGCTT CTGCTGCTCC TGGCGAGTCA
 24801 ACCAACAGAG GATAAAAAGC AAGACCAGGA CAACGCAGAG GCAAACGAGG
 TGGTTGTCTC CTATTTTTCG TTCTGGTCTT GTTGCCTCTC CGTTTGCTCC
 24851 AACAAAGTCGG GCGGGGGGAC GAAAGGCATG GCGACTACCT AGATGTGGGA
 TTGTTTCAGCC CGCCCCCTG CTTTCCGTAC CGCTGATGGA TCTACACCTT
 24901 GACGACGTGC TGTTGAAGCA TCTGCAGCGC CAGTGCGCCA TTATCTGCGA
 CTGCTGCACG ACAACTTTCG AGACGTCGCG GTCACGCGGT AATAGACGCT
 24951 CGCGTTGCAA GAGCGCAGCG ATGTGCCCCCT CGCCATAGCG GATGTCAGCC
 GCGCAACGTT CTCGCGTCGC TACACGGGGA GCGGTATCGC CTACAGTCGG
 25001 TTGCCTACGA ACGCCACCTA TTCTACCGC GCGTACCCCC CAAACGCCAA
 AACGGATGCT TCGGGTGGAT AAGAGTGGCG CGCATGGGGG GTTTGCGGTT
 25051 GAAAACGGCA CATGCGAGCC CAACCCGCGC CTCAACTTCT ACCCGTATT
 CTTTTGCCGT GTACGCTCGG GTTGGGCGCG GAGTTGAAGA TGGGGCATAA
 25101 TGCCGTGCCA GAGGTGCTTG CCACCTATCA CATCTTTTTC CAAAACCTGCA
 ACGGCACGGT CTCCACGAAC GGTGGATAGT GTAGAAAAAG GTTTTGACGT
 25151 AGATACCCCT ATCCTGCCGT GCCAACCACA GCGGAGCGGA CAAGCAGCTG
 TCTATGGGGA TAGGACGGCA CGGTGGCGT CGGCTCGCCT GTTCGTCGAC
 25201 GCCTTGCGGC AGGGCGCTGT CATACTGAT ATCGCCTCGC TCAACGAAGT
 CGGAACGCCG TCCCGCGACA GTATGGACTA TAGCGGAGCG AGTTGCTTCA
 25251 GCCAAAAATC TTTGAGGGTC TTGGACGCGA CGAGAAGCGC GCGGCAAACG
 CGGTTTTTAG AAACCTCCAG AACCTGCGCT GCTCTTCGCG CGCCGTTTGC
 25301 CTCTGCAACA GGAAAACAGC GAAAATGAAA GTCACTCTGG AGTGTGTTGGT
 GAGACGTTGT CTTTTGTGCG CTTTACTTT CAGTGAGACC TCACAACCAC
 25351 GAACTCGAGG GTGACAACGC GCGCCTAGCC GACTAAAAC GCAGCATCGA
 CTTGAGCTCC CACTGTTGCG CGCGGATCGG CATGATTTTG CGTCGTAGCT
 25401 GGTCACCCAC TTTGCCTACC CGGCACTTAA CCTACCCCCC AAGGTCATGA
 CCAGTGGGTG AAACGGATGG GCCGTGAATT GGATGGGGG TTCCAGTACT
 25451 GCACAGTCAT GAGTGAGCTG ATCGTGCGCC GTGCGCAGCC CCTGGAGAGG
 CGTGTCAGTA CTCACTCGAC TAGCACGCGG CACGCGTCGG GGACCTCTCC
 25501 GATGCAAATT TGCAAGAACA AACAGAGGAG GGCCTACCCG CAGTTGGCGA
 CTACGTTTAA ACGTTCTTGT TTGTCTCCTC CCGGATGGGC GTCAACCGCT
 25551 CGAGCAGCTA GCGCGCTGGC TTCAAACGCG CGAGCCTGCC GACTTGGAGG
 GCTCGTCGAT CGCGCGACCG AAGTTTGGCG GCTCGGACGG CTGAACCTCC

Figure 26 AA

25651 TGCATGCAGC GGTTCCTTGC TGACCCGGAG ATGCAGCGCA AGCTAGAGGA
 ACGTACGTCTG CCAAGAAACG ACTGGGCCCTC TACGTCTGCGT TCGATCTCCT

25701 AACATTGCAC TACACCTTTC GACAGGGCTA CGTACGCCAG GCCTGCAAGA
 TTGTAACGTG ATGTGGAAAG CTGTCCCGAT GCATGCGGTC CGGACGTTCT

25751 TCTCCAACGT GGAGCTCTGC AACCTGGTCT CCTACCTTGG AATTTTGCAC
 AGAGGTTGCA CCTCGAGACG TTGGACCAGA GGATGGAACC TTA AACGTG

25801 GAAAACCGCC TTGGGCAAAA CGTGCTTCAT TCCACGCTCA AGGGCGAGGC
 CTTTTGGCGG AACCCGTTTT GCACGAAAGTA AGGTGCGAGT TCCCGCTCCG

25851 GCGCCGCGAC TACGTCCGCG ACTGCGTTTA CTTATTTCTA TGCTACACCT
 CGCGGCGCTG ATGCAGGCGC TGACGCAAAAT GAATAAAGAT ACGATGTGGA

25901 GGCAGACGGC CATGGGCGTT TGGCAGCAGT GCTTGGAGGA GTGCAACCTC
 CCGTCTGCCG GTACCCGCAA ACCGTCGTCA CGAACCTCCT CACGTGTGGAG

25951 AAGGAGCTGC AGAAACTGCT AAAGCAAAAC TTGAAGGACC TATGGACGGC
 TTCTCGACG TCTTTGACGA TTTCGTTTTG AACTTCCTGG ATACCTGCCG

26001 CTTCAACGAG CGCTCCGTGG CCGCGCACCT GCGGGACATC ATTTTCCCCG
 GAAGTTGCTC GCGAGGCACC GCGCGGTGGA CCGCCTGTAG TAAAAGGGGC

26051 AACGCCTGCT TAAAACCCCTG CAACAGGGTC TGCCAGACTT CACCAGTCAA
 TTGCGGACGA ATTTTGGGAC GTTGTCCTAG ACGGTCTGAA GTGGTCAGTT

26101 AGCATGTTGC AGAACTTTAG GAACTTTATC CTAGAGCGCT CAGGAATCTT
 TCGTACAACG TCTTGAAATC CTTGAAATAG GATCTCGCGA GTCTTAGAA

26151 GCCCCGCCACC TGCTGTGCAC TTCCTAGCGA CTTTGTGCCC ATTAAGTACC
 CGGGCGGTGG ACGACACGTG AAGGATCGCT GAAACACGGG TAATTCATGG

26201 GCGAATGCCC TCCGCCGCTT TGGGGCCACT GCTACCTTCT GCAGCTAGCC
 CGCTTACGGG AGGCGGCGAA ACCCCGGTGA CGATGGAAGA CGTCGATCGG

26251 AACTACCTTG CCTACCACTC TGACATAATG GAAGACGTGA GCGGTGACGG
 TTGATGGAAC GGATGGTGAG ACTGTATTAC CTTCTGCACT CGCCACTGCC

26301 TCTACTGGAG TGTCACGTGC GCTGCAACCT ATGCACCCCG CACCGCTCCC
 AGATGACCTC ACAGTGACAG CGACGTTGGA TACGTGGGGC GTGGCGAGGG

26351 TGGTTTGCAA TTCGCAGCTG CTTAACGAAA GTCAAATTAT CGGTACCTTT
 ACCAAACGTT AAGCGTCGAC GAATTGCTTT CAGTTTAATA GCCATGGAAA

26401 GAGCTGCAGG GTCCCTCGCC TGACGAAAAG TCCGCGGCTC CGGGGTGGA
 CTCGACGTCC CAGGGAGCGG ACTGCTTTTC AGGCGCCGAG GCCCAACTT

26451 ACTCACTCCG GGGCTGTGGA CGTCGGCTTA CCTTCGCAA TTTGTACCTG
 TGAGTGAGGC CCCGACACCT GCAGCCGAAT GGAAGCGTTT AAACATGGAC

26501 AGGACTACCA CGCCACGAG ATTAGGTTCT ACGAAGACCA ATCCCGCCCCG
 TCCTGATGGT GCGGGTGCTC TAATCCAAGA TGCTTCTGGT TAGGGCGGGC

Figure 26 AB

26551 CCTAA1 GG AGCTTACCGC CTGCGTCATT ACCCA1 2C ACATTCTTGG
 GGATTACGCC TCGAATGGCG GACGCAGTAA TGGGTCCCCG TGTAAGAACC

26601 CCAATTGCAA GCCATCAACA AAGCCCGCCA AGAGTTTCTG CTACGAAAGG
 GGTTAACGTT CGGTAGTTGT TTCGGGCGGT TCTCAAAGAC GATGCTTTCC

26651 GACGGGGGGT TTACTTGGAC CCCAGTCCG GCGAGGAGCT CAACCCAATC
 CTSCCCCCCA AATGAACCTG GGGGTCAGGC CGCTCCTCGA GTTGGGTTAG

26701 CCCCCCGCGC CGCAGCCCTA TCAGCAGCAG CCGCGGGCCC TTGCTTCCCA
 GGGGGCGGCG GCGTCGGGAT AGTCGTCGTC GGCGCCCGGG AACGAAGGGT

26751 GGATGGCACC CAAAAAGAAG CTGCAGCTGC CGCCGCCACC CACGGACGAG
 CCTACCGTGG GTTTTTCTTC GACGTCGACG GCGGCGGTGG GTGCCTGCTC

26801 GAGGAATACT GGGACAGTCA GGCAGAGGAG GTTTTGGACG AGGAGGAGGA
 CTCTTATGA CCCTGTCAGT CCGTCTCCTC CAAAACCTGC TCCTCCTCCT

26851 GGACATGATG GAAGACTGGG AGAGCCTAGA CGAGGAAGCT TCCGAGGTCTG
 CCTGTACTAC CTTCTGACCC TCTCGGATCT GCTCCTTCGA AGGCTCCAGC

26901 AAGAGGTGTC AGACGAAACA CCGTCACCTT CCGTCGCATT CCCCTCGCCG
 TTCTCCACAG TCTGCTTTGT GGCAGTGGGA GCCAGCGTAA GGGGAGCGGC

26951 GCGCCCCAGA AATCGGCAAC CGGTTCAGC ATGGCTACAA CCTCCGCTCC
 CGCGGGGTCT TTAGCCGTTG GCCAAGGTCG TACCGATGTT GGAGGCGAGG

27001 TCAGGCGCCG CCGGCACTGC CCGTTCGCCG ACCCAACCGT AGATGGGACA
 AGTCCGCGGC GGCCGTGACG GGCAAGCGGC TGGGTTGGCA TCTACCCTGT

27051 CCACTGGAAC CAGGGCCGGT AAGTCCAAGC AGCCGCCGCC GTTAGCCCAA
 GGTGACCTTG GTCCCGGCCA TTCAGGTTCTG TCGGCGGCGG CAATCGGGTT

27101 GAGCAACAAC AGCGCCAAGG CTACCGCTCA TGGCGCGGGC ACAAGAACGC
 CTCGTTGTTG TCGCGGTTCC GATGGCGAGT ACCGCGCCCG GTTCTTTGCG

27151 CATAGTTGCT TGCTTGCAAG ACTGTGGGGG CAACATCTCC TTCGCCGCC
 GTATCAACGA ACGAACGTTT TGACACCCCC GTTGTAGAGG AAGCGGGCGG

27201 GCTTTCTTCT CTACCATCAC GGCCTGGCCT TCCCCGTAA CATCCTGCAT
 CGAAAGAAGA GATGGTAGTG CCGCACCGGA AGGGGGCATT GTAGGACGTA

27251 TACTACCGTC ATCTCTACAG CCCATACTGC ACCGGCGGCA GCGGCAGCAA
 ATGATGGCAG TAGAGATGTC GGGTATGACG TGGCCGCCGT CGCCGTCGTT

27301 CAGCAGCGGC CACACAGAAG CAAAGGCGAC CGGATAGCAA GACTCTGACA
 GTCGTCGCCG GTGTGTCTTC GTTTCCGCTG GCCTATCGTT CTGAGACTGT

27351 AAGCCCAAGA AATCCACAGC GGCGGCAGCA GCAGGAGGAG GAGCGCTGCG
 TTCGGGTTCT TTAGGTGTCT CCGCCGTCGT CGTCCTCCTC CTCGCGACGC

27401 TCTGGCGCCC AACGAACCCG TATCGACCCG CGAGCTTAGA AACAGGATTT
 AGACCGCGGG TTGCTTGGGC ATAGCTGGGC GCTCGAATCT TTGTCCTAAA

27451 TTCCCACTCT GTATGCTATA TTTCAACAGA GCAGGGGCCA AGAACAAGAG
 AAGGGTGAGA CATACGATAT AAAGTTGTCT CGTCCCCGGT TCTTGTCTCT

Figure 26: AC

27551 TCACAAAAGC GAAGATCAGC TTCGGCGCAC GCTGGAAGAC GCGGAGGCTC
 AGTGTTTTCG CTTCTAGTCG AAGCCGCGTG CGACCTTCTG CGCCTCCGAG

27601 TCTTCAGTAA ATACTGCGCG CTGACTCTTA AGGACTAGTT TCGCGCCCTT
 AGAAGTCATT TATGACGCGC GACTGAGAAT TCCTGATCAA AGCGCGGGAA

27651 TCTCAAATTT AAGCGCGAAA ACTACGTCAT CTCCAGCGGC CACACCCGGC
 AGAGTTTAAA TTCGCGCTTT TGATGCAGTA GAGGTCGCCG GTGTGGGCCG

27701 GCCAGCACCT GTTGTCAGCG CCATTATGAG CAAGGAAATT CCCACGCCCT
 CGGTGCTGGA CAACAGTCGC GGTAATACTC GTTCCTTTAA GGGTGCGGGA

27751 ACATGTGGAG TTACCAGCCA CAAATGGGAC TTGCGGCTGG AGCTGCCCAA
 TGTACACCTC AATGGTCGGT GTTTACCCTG AACGCCGACC TCGACGGGTT

27801 GACTACTCAA CCCGAATAAA CTACATGAGC GCGGGACCCC ACATGATATC
 CTGATGAGTT GGGCTTATTT GATGTACTCG CGCCCTGGGG TGTACTATAG

27851 CCGGGTCAAC GGAATACGCG CCCACCGAAA CCGAATTCTC CTGGAACAGG
 GGCCAGTTG CCTTATGCGC GGGTGGCTTT GGCTTAAGAG GACCTTGTC

27901 CGGCTATTAC CACCACACCT CGTAATAACC TTAATCCCCG TAGTTGGCCC
 GCCGATAATG GTGGTGTGGA GCATTATTGG AATTAGGGGC ATCAACCGGG

27951 GCTGCCCTGG TGTACCAGGA AAGTCCCGCT CCCACCACTG TGGTACTTCC
 CGACGGGACC ACATGGTCCT TTCAGGGCGA GGGTGGTGAC ACCATGAAGG

28001 CAGAGACGCC CAGGCCGAAG TTCAGATGAC TAACTCAGGG GCGCAGCTTG
 GTCTCTGCGG GTCCGGCTTC AAGTCTACTG ATTGAGTCCC CGCGTCGAAC

28051 CGGGCGGCTT TCGTCACAGG GTGCGGTGCG CCGGGCAGGG TATAACTCAC
 GCGCGCGAA AGCAGTGTCC CACGCCAGCG GGCCCGTCCC ATATTGAGTG

28101 CTGACAATCA GAGGGCGAGG TATTCAGCTC AACGACGAGT CGGTGAGCTC
 GACTGTTAGT CTCCCGCTCC ATAAGTCGAG TTGCTGCTCA GCCACTCGAG

28151 CTCGCTTGGT CTCCGTCCGG ACGGGACATT TCAGATCGGC GGCGCCGGCC
 GAGCGAACCA GAGGCAGGCC TGCCCTGTAA AGTCTAGCCG CCGCGGCCGG

28201 GCTCTTCATT CACGCCTCGT CAGGCAATCC TAACTCTGCA GACCTCGTCC
 CGAGAAGTAA GTGCGGAGCA GTCCGTTAGG ATTGAGACGT CTGGAGCAGG

28251 TCTGAGCCGC GCTCTGGAGG CATTGGAACT CTGCAATTTA TTGAGGAGTT
 AGACTCGGCG CGAGACCTCC GTAACCTTGA GACGTTAAAT AACTCCTCAA

28301 TGTGCCATCG GTCTACTTTA ACCCCTTCTC GGGACCTCCC GGCCACTATC
 ACACGGTAGC CAGATGAAAT TGGGGAAGAG CCCTGGAGGG CCGGTGATAG

28351 CGGATCAATT TATTCCTAAC TTTGACGCGG TAAAGGACTC GCGCGACGGC
 GCCTAGTTAA ATAAGGATTG AAAGTGCGCC ATTTCTCTGAG CCGCTGCGG

28401 TACGACTGAA TGTAAAGTGG AGAGGCAGAG CAACTGCGCC TGAAACACCT
 ATGCTGACTT ACAATTCACC TCTCCGTCTC GTTGACGCGG ACTTTGTGGA

Figure 26 AD

28451 GGTCCAC...GT CGCCGCCACA AGTGCTTTGC CCGCGA...C GGTGAGTTT
 CCAGGTGACA GCGGCGGTGT TCACGAAACG GCGCTGAGG CCACTCAAAA

 28501 GCTACTTTGA ATTGCCGAG GATCATATCG AGGGCCCGGC GCACGGCGTC
 CGATGAAACT TAACGGGCTC CTAGTATAGC TCCCGGGCCG CGTGCCCGAG

 28551 CGGCTTACCG CCCAGGGAGA GCTTGCCCGT AGCCTGATTC GGGAGTTTAC
 GCCGAATGGC GGGTCCCTCT CGAACGGGCA TCGGACTAAG CCCTCAAATG

 28601 CCAGCGCCCC CTGCTAGTTG AGCGGGACAG GGGACCCTGT GTTCTCACTG
 GGTGCGGGG GACGATCAAC TCGCCCTGTC CCCTGGGACA CAAGAGTGAC

 28651 TGATTTGCAA CTGTCCTAAC CCTGGATTAC ATCAAGATCT TTGTTGCCAT
 ACTAAACGTT GACAGGATTG GGACCTAATG TAGTTCTAGA AACACCGTA

 28701 CTCTGTGCTG AGTATAATAA ATACAGAAAT TAAATATAC TGGGGCTCCT
 GAGACACGAC TCATATTATT TATGTCTTTA ATTTTATATG ACCCCGAGGA

 28751 ATCGCCATCC TGTAACGCC ACCGTCTTCA CCCGCCAAG CAAACCAAGG
 TAGCGGTAGG ACATTGCGG TGGCAGAAGT GGGCGGGTTC GTTGGTTCC

 28801 CGAACCTTAC CTGGTACTTT TAACATCTCT CCCTCTGTGA TTTACAACAG
 GCTTGGAATG GACCATGAAA ATTGTAGAGA GGGAGACACT AAATGTTGTC

 28851 TTTCAACCCA GACGGAGTGA GTCTACGAGA GAACCTCTCC GAGCTCAGCT
 AAAGTTGGGT CTGCCTCACT CAGATGCTCT CTTGGAGAGG CTCGAGTCGA

 28901 ACTCCATCAG AAAAAACACC ACCCTCCTTA CCTGCCGGGA ACGTACGAGT
 TGAGGTAGTC TTTTTGTGG TGGGAGGAAT GGACGGCCCT TGCATGCTCA

 28951 GCGTCACCGG CCGCTGCACC ACACCTACCG CCTGACCGTA AACCAGACTT
 CGCAGTGGCC GGCACGTGG TGTGGATGGC GGACTGGCAT TTGGTCTGAA

 29001 TTTCCGGACA GACCTCAATA ACTCTGTTTA CCAGAACAGG AGGTGAGCTT
 AAAGGCCTGT CTGGAGTTAT TGAGACAAAT GGTCTTGTCC TCCACTCGAA

 29051 AGAAAACCTT TAGGGTATTA GGCCAAAGGC GCAGCTACTG TGGGGTTTAT
 TCTTTTGGGA ATCCCATAAT CCGGTTTCCG CGTCGATGAC ACCCCAAATA

 29101 GAACAATTCA AGCAACTCTA CGGGCTATTC TAATTCAGGT TTCTCTAGAA
 CTTGTTAAGT TCGTTGAGAT GCCCGATAAG ATTAAGTCCA AAGAGATCTT

 29151 TCGGGGTTGG GGTATTCTC TGTCTTGTA TTCTCTTTAT TCTTATACTA
 AGCCCCAACC CCAATAAGAG ACAGAACACT AAGAGAAATA AGAATATGAT

 29201 ACGCTTCTCT GCCTAAGGCT CGCCGCCCTGC TGTGTGCACA TTTGCATTTA
 TCGCAAGAGA CGGATTCCGA GCGGCGGACG ACACACGTGT AAACGTAAAT

 29251 TTGTCAGCTT TTAAACGCT GGGGTCGCCA CCCAAGATGA TTAGGTACAT
 AACAGTCGAA AAATTTGCGA CCCCAGCGGT GGGTTCTACT AATCCATGTA

 29301 AATCCTAGGT TTAATCAGCT TTGCGTCAGC CCACGGTACC ACCCAAAGG
 TTAGGATCCA AATGAGTGGG AACGCAGTCG GGTGCCATGG TGGGTTTTCC

 29351 TGGATTTTAA GGAGCCAGCC TGTAATGTTA CATTCGCAGC TGAAGCTAAT
 ACCTAAAATT CCTCGGTCGG ACATTACAAT GTAAGCGTCG ACTTCGATTA

Figure 26 AE

29451 TCGCCACAAA AACAAAATTG GCAAGTATGC TGTTTATGCT ATTTGGGCAGC
 AGCGGTGTTT TTGTTTAAAC CGTTCATACG ACAAATACGA TAAACCGTCG
 29501 CAGGTGACAC TACAGAGTAT AATGTTACAG TTTTCCAGGG TAAAAGTCAT
 GTCCACTGTG ATGTCTCATA TTACAATGTC AAAAGGTCCC ATTTTCAGTA
 29551 AAAACTTTTA TGTATACTTT TCCATTTTAT GAAATGTGCG ACATTACCAT
 TTTTGAAAAAT ACATATGAAA AGGTAAAAATA CTTTACACGC TGTAATGGTA
 29601 GTACATGAGC AAACAGTATA AGTTGTGGCC CCCACAAAAT TGTGTGGAAA
 CATGTACTCG TTTGTCATAT TCAACACCGG GGGTGTTTTA ACACACCTTT
 29651 ACACTGGCAC TTTCTGCTGC ACTGCTATGC TAATTACAGT GCTCGCTTTG
 TGTGACCGTG AAAGACGACG TGACGATACG ATTAATGTCA CGAGCGAAAC
 29701 GTCTGTACCC TACTCTATAT TAAATACAAA AGCAGACGCA GCTTTATTGA
 CAGACATGGG ATGAGATATA ATTTATGTTT TCGTCTGCGT CGAAATAACT
 29751 GGAAAAGAAA ATGCCTTAAT TTAATAAGTT ACAAAGCTAA TGTCACCACT
 CCTTTTCTTT TACGGAATTA AATGATTCAA TGTTTCGATT ACAGTGGTGA
 29801 AACTGCTTTA CTCGCTGCTT GCAAAACAAA TTCAAAAAGT TAGCATTATA
 TTGACGAAAT GAGCGACGAA CGTTTTGTTT AAGTTTTTCA ATCGTAATAT
 29851 ATTAGAATAG GATTTAACC CCCC GGTCAT TTCCTGCTCA ATACCATTCC
 TAATCTTATC CTAAATTTGG GGGGCCAGTA AAGGACGAGT TATGGTAAGG
 29901 CCTGAACAAT TGACTCTATG TGGGATATGC TCCAGCGCTA CAACCTTGAA
 GGACTTGTTA ACTGAGATAC ACCCTATACG AGGTCGCGAT GTTGGAACCT
 29951 GTCAGGCTTC CTGGATGTCA GCATCTGACT TTGGCCAGCA CCTGTCCCGC
 CAGTCCGAAG GACCTACAGT CGTAGACTGA AACCGGTCGT GGACAGGGCG
 30001 GGATTTGTTT CAGTCCAAC ACACGCGACCC ACCCTAACAG AGATGACCAA
 CCTAAACAAG GTCAGGTTGA TGTCGCTGGG TGGGATTGTC TCTACTGGTT
 30051 CACAACCAAC GCGGCCGCCG CTACCGGACT TACATCTACC ACAAATACAC
 GTGTTGGTTG CGCCGGCGGC GATGGCCTGA ATGTAGATGG TGTTTATGTG
 30101 CCCAAGTTTC TGCTTTTGTC AATAACTGGG ATAACCTGGG CATGTGGTGG
 GGGTTCAAAG ACGGAAACAG TTATTGACCC TATTGAACCC GTACACCACC
 30151 TTCTCCATAG CGCTTATGTT TGTATGCCTT ATTATTATGT GGCTCATCTG
 AAGAGGTATC GCGAATACAA ACATACGGAA TAATAATACA CCGAGTAGAC
 30201 CTGCCTAAAG CGCAAACGCG CCCGACCACC CATCTATAGT CCCATCATTG
 GACGGATTTT GCGTTTGCGC GGGCTGGTGG GTAGATATCA GGGTAGTAAC
 30251 TGCTACACCC AAACAATGAT GGAATCCATA GATTGGACGG ACTGAAACAC
 ACGATGTGGG TTTGTTACTA CCTTAGGTAT CTAACCTGCC TGACTTTGTG
 30301 ATGTTCTTTT CTCTTACAGT ATGATTAAAT GAGACATGAT TCCTCGAGTT
 TACAAGAAAA GAGAATGTCA TACTAATTTA CTCTGTACTA AGGAGCTCAA

Figure 26 AF

30401 TCGGGTTTCT CACATCGAAG TAGACTGCAT TCCAGCCTTC ACAGTCTATT
ACGCCAAAGA GTGTAGCTTC ATCTGACGTA AGGTCGGAAG TGTCAGATAA

30451 TGCTTTACGG ATTTGTCACC CTCACGCTCA TCTGCAGCCT CATCACTGTG
ACGAAATGCC TAAACAGTGG GAGTGCAGT AGACGTCGGA GTAGTGACAC

30501 GTCATCGCCT TTATCCAGTG CATTGACTGG GTCTGTGTGC GCTTTGCATA
CAGTAGCGGA AATAGGTCAC GTAAGTACC CAGACACACG CGAAACGTAT

30551 TCTCAGACAC CATCCCCAGT ACAGGGACAG GACTATAGCT GAGCTTCTTA
AGAGTCTGTG GTAGGGGTCA TGTCCCTGTC CTGATATCGA CTCGAAGAAT

30601 GAATTCTTTA ATTATGAAAT TTAAGTGTGAC TTTTCTGCTG ATTATTTGCA
CTTAAGAAAT TAATACTTTA AATGACACTG AAAAGACGAC TAATAAACGT

30651 CCCTATCTGC GTTTTGTTC CCGACCTCCA AGCCTCAAAG ACATATATCA
GGGATAGACG CAAAACAAGG GGCTGGAGGT TCGGAGTTTC TGTATATAGT

30701 TGCAGATTCA CTCGTATATG GAATATTCCA AGTTGCTACA ATGAAAAAAG
ACGTCTAAGT GAGCATATAC CTTATAAGGT TCAACGATGT TACTTTTTTC

30751 CGATCTTTTC GAAGCCTGGT TATATGCAAT CATCTCTGTT ATGGTGTCTT
GCTAGAAAGG CTTTCGGACCA ATATACGTTA GTAGAGACAA TACCACAAGA

30801 GCAGTACCAT CTTAGCCCTA GCTATATATC CCTACCTTGA CATTGGCTGG
CGTCATGGTA GAATCGGGAT CGATATATAG GGATGGAAC GTAAACCGACC

30851 AACGCAATAG ATGCCATGAA CCACCCAACT TTCCCCGCGC CCGCTATGCT
TTGCGTTATC TACGGTACTT GGTGGGTTGA AAGGGGCGCG GGCGATACGA

30901 TCCACTGCAA CAAGTTGTTG CCGGCGGCTT TGTCCCAGCC AATCAGCCTC
AGGTGACGTT GTTCAACAAC GGCCGCCGAA ACAGGGTCGG TTAGTCGGAG

30951 GCCCACCTTC TCCCACCCCC ACTGAAATCA GCTACTTTAA TCTAACAGGA
CGGGTGGAAG AGGGTGGGGG TGACTTTAGT CGATGAAATT AGATTGTCTT

31001 GGAGATGACT GACACCCTAG ATCTAGAAAT GGACGGAATT ATTACAGAGC
CCTCTACTGA CTGTGGGATC TAGATCTTTA CCTGCCTTAA TAATGTCTCG

31051 AGCGCCTGCT AGAAAGACGC AGGGCAGCGG CCGAGCAACA GCGCATGAAT
TCGCGGACGA TCTTTCTGCG TCCCGTCGCC GGCTCGTTGT CGCGTACTTA

31101 CAAGAGCTCC AAGACATGGT TAACTTGCAC CAGTGCAAAA GGGGTATCTT
GTTCTCGAGG TTCTGTACCA ATTGAACGTG GTCACGTTTT CCCCATAGAA

31151 TTGTCTCGTA AAGCAGGCCA AAGTCACCTA CGACAGTAAT ACCACCGGAC
AACAGAGCAT TTCGTCCGGT TTCAGTGGAT GCTGTCTATTA TGGTGGCCTG

31201 ACCGCCTTAG CTACAAGTTG CCAACCAAGC GTCAGAAATT GGTGGTCATG
TGGCGGAATC GATGTTCAAC GGTGTTGTCG CAGTCTTTAA CCACAGTAC

31251 GTGGGAGAAA AGCCCATAC CATAACTCAG CACTCGGTAG AAACCGAAGG
CACCTCTTT TCGGGTAATG GTATTGAGTC GTGAGCCATC TTTGGCTTCC

Figure 26 AG

31351 AGACCCCTGTG CGGTCTCAAA GATCTTATTC CCTTTAACTA ATAAAAAAAA
TCTGGGACAC GCCAGAGTTT CTAGAATAAG GGAAATTGAT TATTTTTTTT

31401 ATAATAAAGC ATCACTTACT TAAAATCAGT TAGCAAATTT CTGTCCAGTT
TATTATTTTCG TAGTGAATGA ATTTTAGTCA ATCGTTTAAA GACAGGTCAA

31451 TATTCAGCAG CACCTCCTTG CCCTCCTCCC AGCTCTGGTA TTGCAGCTTC
ATAAGTCGTC GTGGAGGAAC GGGAGGAGGG TCGAGACCAT AACGTCGAAG

31501 CTCCTGGCTG CAAACTTTCT CCACAATCTA AATGGAATGT CAGTTTCCTC
GAGGACCGAC GTTTGAAAGA GGTGTTAGAT TTACCTTACA GTCAAAGGAG

31551 CTGTTCTGT CCATCCGCAC CCACTATCTT CATGTTGTTG CAGATGAAGC
GACAAGGACA GGTAGGCGTG GGTGATAGAA GTACAACAAC GTCTACTTCG

31601 GCGCAAGACC GTCTGAAGAT ACCTTCAACC CCGTGTATCC ATATGACACG
CGCGTTCTGG CAGACTTCTA TGGAAGTTGG GGCACATAGG TATACTGTGC

31651 GAAACCGGTC CTCCAACGTG GCCTTTTCTT ACTCCTCCCT TTGTATCCCC
CTTTGGCCAG GAGGTTGACA CGGAAAAGAA TGAGGAGGGA AACATAGGGG

31701 CAATGGGTTT CAAGAGAGTC CCCCTGGGGT ACTCTCTTTG CGCCTATCCG
GTTACCCAAA GTTCTCTCAG GGGGACCCCA TGAGAGAAAC GCGGATAGGC

31751 AACCTCTAGT TACCTCCAAT GGCATGCTTG CGCTCAAAAT GGGCAACGGC
TTGGAGATCA ATGGAGGTTA CCGTACGAAC GCGAGTTTAA CCCGTTGCCG

31801 CTCTCTCTGG ACGAGGCCGG CAACCTTACC TCCCAAAATG TAACCACTGT
GAGAGAGACC TGCTCCGGCC GTTGGAAATGG AGGGTTTTAC ATTGGTGACA

31851 GAGCCCACCT CTCAAAAAA CCAAGTCAAA CATAAACCTG GAAATATCTG
CTCGGGTGGA GAGTTTTTTT GGTTCAGTTT GTATTTGGAC CTTTATAGAC

31901 CACCCCTCAC AGTTACCTCA GAAGCCCTAA CTGTGGCTGC CGCCGCACCT
GTGGGGAGTG TCAATGGAGT CTTGCGGATT GACACCGACG GCGGCGTGGA

31951 CTAATGGTCG CGGGCAACAC ACTCACCATG CAATCACAGG CCCCGCTAAC
GATTACCAGC GCCCGTTGTG TGAGTGGTAC GTTAGTGTCC GGGGCGATTG

32001 CGTGCACGAC TCCAAACTTA GCATTGCCAC CCAAGGACCC CTCACAGTGT
GCACGTGCTG AGGTTTGAAT CGTAACGGTG GGTTCTGGG GAGTGTCAAC

32051 CAGAAGGAAA GCTAGCCCTG CAAACATCAG GCCCCTCAC CACCACCGAT
GTCTTCCTTT CGATCGGGAC GTTTGTAGTC CGGGGGAGTG GTGGTGGCTA

32101 AGCAGTACCC TTACTATCAC TGCCTCACCC CCTCTAACTA CTGCCACTGG
TCGTCATGGG AATGATAGTG ACGGAGTGGG GGAGATTGAT GACGGTGACC

32151 TAGCTTGGGC ATTGACTTGA AAGAGCCCAT TTATACACAA AATGGAAAAC
ATCGAACCCG TAACTGAACT TTCTCGGGTA AATATGTGTT TTACCTTTTG

32201 TAGGACTAAA GTACGGGGCT CCTTTGCATG TAACAGACGA CCTAAACACT
ATCCTGATTT CATGCCCGA GGAAACGTAC ATTGTCTGCT GGATTTGTGA

Figure 26 AH

32301 AACTAAAGTT ACTGGAGCCT TGGGTTTTGA TTCACAAGGC AATATGCAAC
TTGATTTCAA TGACCTCGGA ACCCAAACT AAGTGTTCG TTATACGTTG

32351 TTAATGTAGC AGGAGGACTA AGGATTGATT CTCAAAACAG ACGCCTTATA
AATTACATCG TCCTCCTGAT TCCTAACTAA GAGTTTTGTC TGC GGAATAT

32401 CTTGATGTTA GTTATCCGTT TGATGCTCAA AACCAACTAA ATCTAAGACT
GAACTACAA CAATAGGCAA ACTACGAGTT TTGGTTGATT TAGATTCTGA

32451 AGGACAGGGC CCTCTTTTTA TAACTCAGC CCACAACCTG GATATTAACT
TCCTGTCCCG GGAGAAAAAT ATTTGAGTCG GGTGTTGAAC CTATAATTGA

32501 ACAACAAAGG CCTTTACTTG TTTACAGCTT CAAACAATTC CAAAAAGCTT
TGTTGTTTCC GGAAATGAAC AAATGTCGAA GTTTGTTAAG GTTTTTTCGAA

32551 GAGGTTAACC TAAGCACTGC CAAGGGGTTG ATGTTTGACG CTACAGCCAT
CTCCAATTGG ATTCGTGACG GTTCCCAAC TACAACTGC GATGTCGGTA

32601 AGCCATTAAT GCAGGAGATG GGCTTGAATT TGGTTCACCT AATGCACCAA
TCGGTAATTA CGTCCTCTAC CCGAACTAA ACCAAGTGGA TTACGTGGTT

32651 ACACAAATCC CCTCAAACA AAAATTGGCC ATGGCCTAGA ATTTGATTCA
TGTGTTTAGG GGAGTTTTGT TTTTAACCGG TACCGGATCT TAACTAAGT

32701 AACAAAGGCTA TGGTTCCTAA ACTAGGAAC GGCCTTAGTT TTGACAGCAC
TTGTTCCGAT ACCAAGGATT TGATCCTGA CCGGAATCAA AACTGTCGTG

32751 AGGTGCCATT ACAGTAGGAA ACAAAAATAA TGATAAGCTA ACTTTGTGGA
TCCACGGTAA TGTCATCCTT TGTTTTTATT ACTATTCGAT TGAAACACCT

32801 CCACACCAGC TCCATCTCCT AACTGTAGAC TAAATGCAGA GAAAGATGCT
GGTGTGGTCG AGGTAGAGGA TTGACATCTG ATTTACGTCT CTTTCTACGA

32851 AAACCTCACTT TGGTCTTAAC AAAATGTGGC AGTCAAATAC TTGCTACAGT
TTTGAGTGAA ACCAGAATTG TTTTACACCG TCAGTTTATG AACGATGTCA

32901 TTCAGTTTTG GCTGTTAAAG GCAGTTTGGC TCCAATATCT GGAACAGTTC
AAGTCAAAAC CGACAATTC CGTCAAACCG AGGTTATAGA CCTTGTC AAG

32951 AAAGTGCTCA TCTTATTATA AGATTTGACG AAAATGGAGT GCTACTAAAC
TTTCACGAGT AGAATAATAT TCTAACTGC TTTTACCTCA CGATGATTTG

33001 AATTCCTTCC TGGACCCAGA ATATTGGAAC TTTAGAAATG GAGATCTTAC
TTAAGGAAGG ACCTGGGTCT TATAACCTG AAATCTTTAC CTCTAGAATG

33051 TGAAGGCACA GCCTATACAA ACGCTGTTGG ATTTATGCCT AACCTATCAG
ACTTCCGTGT CGGATATGTT TGC GACAACC TAAATACGGA TTGGATAGTC

33101 CTTATCCAAA ATCTCACGGT AAACTGCCA AAAGTAACAT TGTCAGTCAA
GAATAGGTTT TAGAGTGCCA TTTTGACGGT TTTCATTGTA ACAGTCAGTT

33151 GTTTACTTAA ACGGAGACAA AACTAAACCT GTAACACTAA CCATTACACT
CAAATGAATT TGCCTCTGTT TTGATTTGGA CATTGTGATT GGTAATGTGA

Figure 26 AI

33251 CATTTCATG GGA CTGGTCT GGCCACA ACT ACATTAATGA AATATTTGCC
GTAAAAGTAC CCTGACCAGA CCGGTGTTGA TGTAACTACT TTATAAACGG

33301 ACATCCTCTT ACAC TTTTTC ATACATTGCC CAAGAATAAA GAATCGTTTG
TG TAGGAGAA TGTGAAAAAG TATGTAACGG GTTCTTATTT CTTAGCAAAC

33351 TGT TATGTTT CAACGTGTTT ATTTTTC AAT TGCAGAAAAT TTCAAGTCAT
ACAATACAAA GTTGCACAAA TAAAAAGTTA ACGTCTTTTA AAGTTCAGTA

33401 TTTTCATTCA GTAGTATAGC CCCACCACCA CATAGCTTAT ACAGATCACC
AAAAGTAAGT CATCATATCG GGGTGGTGGT GTATCGAATA TGTCTAGTGG

33451 GTACCTTAAT CAAACTCACA GAACCCTAGT ATTCAACCTG CCACCTCCCT
CATGGAATTA GTTTGAGTGT CTTGGGATCA TAAGTTGGAC GGTGGAGGGA

33501 CCCAACACAC AGAGTACACA GTCCTTTCTC CCCGGCTGGC CTTAAAAAGC
GGGTTGTGTG TCTCATGTGT CAGGAAAGAG GGGCCGACCG GAATTTTTCG

33551 ATCATATCAT GGGTAACAGA CATATTCTTA GGTGTTATAT TCCACACGGT
TAGTATAGTA CCCATTGTCT GTATAAGAAT CCACAATATA AGGTGTGCCA

33601 TTCCTGTCGA GCCAAACGCT CATCAGTGAT ATTAATAAAC TCCCCGGGCA
AAGGACAGCT CGGTTTGCGA GTAGTACTA TAATTATTTG AGGGGCCCGT

33651 GCTCACTTAA GTTCATGTCG CTGTCCAGCT GCTGAGCCAC AGGCTGCTGT
CGAGTGAATT CAAGTACAGC GACAGGTCGA CGACTCGGTG TCCGACGACA

33701 CCAACTTGCG GTTGCTTAAC GGGCGGCGAA GGAGAAGTCC ACGCCTACAT
GGTTGAACGC CAACGAATTG CCCGCCGCTT CCTCTTCAGG TGCGGATGTA

33751 GGGGGTAGAG TCATAATCGT GCATCAGGAT AGGGCGGTGG TGCTGCAGCA
CCCCCATCTC AGTATTAGCA CGTAGTCCTA TCCCGCCACC ACGACGTCGT

33801 GCGCGCGAAT AAAGTGTGC GCGCGCCGCT CCGTCCTGCA GGAATACAAC
CGCGCGCTTA TTTGACGACG GCGGCGGCGA GGCAGGACGT CCTTATGTTG

33851 ATGGCAGTGG TCTCCTCAGC GATGATTGCG ACCGCCCGCA GCATAAGGCG
TACCGTCACC AGAGGAGTCG CTACTAAGCG TGGCGGGCGT CGTATTCCGC

33901 CCTTGTCCTC CGGGCACAGC AGCGCACCTT GATCTCACTT AAATCAGCAC
GGAACAGGAG GCGCGTGTG TCGCGTGGGA CTAGAGTGAA TTTAGTCGTG

33951 AGTAACTGCA GCACAGCACC ACAATATTGT TCAAAATCCC ACAGTGCAAG
TCATTGACGT CGTGTGCTGG TGT TATAACA AGTTTTAGGG TGTCACGTTT

34001 GCGCTGTATC CAAAGCTCAT GCGGGGGACC ACAGAACCCA CGTGGCCATC
CGCGACATAG GTTTCGAGTA CCGCCCCTGG TGTCTTGGGT GCACCGGTAG

34051 ATACCACAAG CGCAGGTAGA TTAAGTGGCG ACCCCTCATA AACACGCTGG
TATGGTGTTC GCGTCCATCT AATTCACCGC TGGGGAGTAT TTGTGCGACC

34101 ACATAAACAT TACCTCTTTT GGCATGTTGT AATTCACCAC CTCCCGGTAC
TGTATTTGTA ATGGAGAAAA CCGTACAACA TTAAGTGGTG GAGGGCCATG

Figure 26 AJ

34201	GCTGGCCAAA	ACCTGCCCGC	CGGCTATACA	CTGCAGGGAA	CCGGGACTGG
	CGACCGGTTT	TGGACGGGCG	GCCGATATGT	GACGTCCCTT	GGCCCTGACC
34251	AACAATGACA	GTGGAGAGCC	CAGGACTCGT	AACCATGGAT	CATCATGCTC
	TTGTTACTGT	CACCTCTCGG	GTCTTGAGCA	TTGGTACCTA	GTAGTACGAG
34301	GTCATGATAT	CAATGTTGGC	ACAACACAGG	CACACGTGCA	TACACTTCCT
	CAGTACTATA	GTTACAACCG	TGTTGTGTCC	GTGTGCACGT	ATGTGAAGGA
34351	CAGGATTACA	AGCTCCTCCC	GCGTTAGAAC	CATATCCCAG	GGAACAACCC
	GTCTTAATGT	TCGAGGAGGG	CGCAATCTTG	GTATAGGGTC	CCTTGTGGG
34401	ATTCTTGAAT	CAGCGTAAAT	CCCACACTGC	AGGGAAGACC	TCGCACGTAA
	TAAGGACTTA	GTCGCATTTA	GGGTGTGACG	TCCCTTCTGG	AGCGTGCATT
34451	CTCACGTTGT	GCATTGTCAA	AGTGTTACAT	TCGGGCAGCA	GCGGATGATC
	GAGTGCAACA	CGTAACAGTT	TCACAATGTA	AGCCCGTCGT	CGCCTACTAG
34501	CTCCAGTATG	GTAGCGCGGG	TTTCTGTCTC	AAAAGGAGGT	AGACGATCCC
	GAGGTCATAC	CATCGCGCCC	AAAGACAGAG	TTTTCTCCA	TCTGCTAGGG
34551	TACTGTACGG	AGTGCGCCGA	GACAACCGAG	ATCGTGTGG	TCGTAGTGTG
	ATGACATGCC	TCACGCGGCT	CTGTTGGCTC	TAGCACAACC	AGCATCACAG
34601	ATGCCAAATG	GAACGCCGGA	CGTAGTCATA	TTTCCTGAAG	CAAAACCAGG
	TACGGTTTAC	CTTGCGGCCT	GCATCAGTAT	AAAGGACTTC	GTTTTGGTCC
34651	TGCGGGCGTG	ACAAACAGAT	CTGCGTCTCC	GGTCTCGCCG	CTTAGATCGC
	ACGCCCAC	TGTTTGTCTA	GACGCAGAGG	CCAGAGCGGC	GAATCTAGCG
34701	TCTGTGTAGT	AGTTGTAGTA	TATCCACTCT	CTCAAAGCAT	CCAGGCGCCC
	AGACACATCA	TCAACATCAT	ATAGGTGAGA	GAGTTTCGTA	GGTCCGCGGG
34751	CCTGGCTTCG	GGTCTATGT	AACTCCTTC	ATGCGCCGCT	GCCCTGATAA
	GGACCGAAGC	CCAAGATACA	TTTGAGGAAG	TACGCGGCGA	CGGGACTATT
34801	CATCCACCAC	CGCAGAATAA	GCCACACCCA	GCCAACCTAC	ACATTCTGTC
	GTAGGTGGTG	GCGTCTTATT	CGGTGTGGGT	CGGTTGGATG	TGTAAGCAAG
34851	TGCGAGTCAC	ACACGGGAGG	AGCGGGAAGA	GCTGGAAGAA	CCATGTTTTT
	ACGCTCAGTG	TGTGCCCTCC	TCGCCCTTCT	CGACCTTCTT	GGTACAAAAA
34901	TTTTTTATTTC	CAAAAGATTA	TCCAAAACCT	CAAAATGAAG	ATCTATTAAG
	AAAAAATAAG	GTTTTCTAAT	AGGTTTTTGA	GTTTTACTTC	TAGATAATTC
34951	TGAACGCGCT	CCCCTCCGGT	GGCGTGGTCA	AACCTTACAG	CCAAAGAACA
	ACTTGCGCGA	GGGGAGGCCA	CCGCACCAGT	TTGAGATGTC	GGTTTCTTGT
35001	GATAATGGCA	TTTGTAAGAT	GTTGCACAAT	GGCTTCCAAA	AGGCAAACGG
	CTATTACCGT	AAACATTCTA	CAACGTGTTA	CCGAAGGTTT	TCCGTTTGCC
35051	CCCTCACGTC	CAAGTGGACG	TAAAGGCTAA	ACCTTCAGG	GTGAATCTCC
	GGGAGTGCAG	GTTACCTGTC	ATTTCCGATT	TGGGAAGTCC	CACTTAGAGG

Figure 26 AK


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35151 CCACCTTCTC AATATATCTC TAAGCAAATC CCGAATATTA AGTCCGGCCA
      GGTGGAAGAG TTATATAGAG ATTCGTTTAG GGCTTATAAT TCAGGCCGGT

35201 TTGTAAAAAT CTGCTCCAGA GCGCCCTCCA CCTTCAGCCT CAAGCAGCGA
      AACATTTTAA GACGAGGTCT CGCGGGAGGT GGAAGTCGGA GTTCGTCGCT

35251 ATCATGATTG CAAAAATTCA GGTTCCTCAC AGACCTGTAT AAGATTCAAA
      TAGTACTAAC GTTTTAAAGT CCAAGGAGTG TCTGGACATA TTCTAAGTTT

35301 AGCGGAACAT TAACAAAAAT ACCGCGATCC CGTAGGTCCC TTCGCAGGGC
      TCGCCTTGTA ATTGTTTTTA TGGCGCTAGG GCATCCAGGG AAGCGTCCCC

35351 CAGCTGAACA TAATCGTGCA GGTCTGCACG GACCAGCGCG GCCACTTCCC
      GTCGACTTGT ATTAGCACGT CCAGACGTGC CTGGTCGCGC CCGTGAAGGG

35401 CGCCAGGAAC CATGACAAAA GAACCCACAC TGATTATGAC ACGCATACTC
      GCGGTCCTTG GTACTGTTTT CTTGGGTGTG ACTAATACTG TCGGTATGAG

35451 GGAGCTATGC TAACCAGCGT AGCCCCGATG TAAGCTTGTT GCATGGGCGG
      CCTCGATACG ATTGGTCGCA TCGGGGCTAC ATTCGAACAA CGTACCCGCC

35501 CGATATAAAA TGCAAGGTGC TGCTCAAAAA ATCAGGCAAA GCCTCGCGCA
      GCTATATTTT ACGTTCCACG ACGAGTTTTT TAGTCCGTTT CGGAGCGCGT

35551 AAAAAAGAAAG CACATCGTAG TCATGCTCAT GCAGATAAAG GCAGGTAAGC
      TTTTCTTTTC GTGTAGCATC AGTACGAGTA CGTCTATTTC CGTCCATTTC

35601 TCCGGAACCA CCACAGAAAA AGACACCATT TTTCTCTCAA ACATGTCTGC
      AGGCCTTGGT GGTGTCTTTT TCTGTGGTAA AAAGAGAGTT TGTACAGACG

35651 GGGTTTCTGC ATAAACACAA AATAAAATAA CAAAAAACA TTTAAACATT
      CCCAAAGACG TATTTGTGTT TTATTTTATT GTTTTTTTGT AAATTTGTAA

35701 AGAAGCCTGT CTTACAACAG GAAAAACAAC CCTTATAAGC ATAAGACGGA
      TCTTCGGACA GAATGTTGTC CTTTTTGTG GGAATATTTC TATTCTGCCT

35751 CTACGGCCAT GCCGGCGTGA CCGTAAAAAA ACTGGTCACC GTGATTAAAA
      GATGCCGGTA CGGCCGCACT GGCATTTTTT TGACCAGTGG CACTAATTTT

35801 AGCACCACCG ACAGCTCCTC GGTCAATGCC GGAGTCATAA TGTAAGACTC
      TCGTGGTGGC TGTCGAGGAG CCAGTACAGG CCTCAGTATT ACATTCTGAG

35851 GGTAAACACA TCAGGTTGAT TCACATCGGT CAGTGCTAAA AAGCGACCGA
      CCATTTGTGT AGTCCAACATA AGTGTAGCCA GTCACGATTT TTCGCTGGCT

35901 AATAGCCCGG GGGAATACAT ACCCGCAGGC GTAGAGACAA CATTACAGCC
      TTATCGGGCC CCCTTATGTA TGGGCGTCCG CATCTCTGTT GTAATGTCGG

35951 CCCATAGGAG GTATAACAAA ATTAATAGGA GAGAAAAACA CATAAACACC
      GGGTATCCTC CATATTGTTT TAATTATCCT CTCTTTTGT GTATTGTGG

36001 TGAAAAACCC TCCTGCCTAG GCAAAATAGC ACCCTCCCGC TCCAGAACAA
      ACTTTTTGGG AGGACGGATC CGTTTTATCG TGGGAGGGCG AGGTCTTGTT

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Figure 26 AL

36101 AAAGAAAACC TATTAATAAA ACACCACTCG ACACGGCACC AGCTCAATCA
 TTTCTTTTGG ATAATTTTTT TGTGGTGAGC TGCGCCGTGG TCGAGTTAGT

36151 GTCACAGTGT AAAAAAGGGC CAAGTGCAGA GCGAGTATAT ATAGGACTAA
 CAGTGTACACA TTTTTTCCCG GTTCACGTCT CGCTCATATA TATCCTGATT

36201 AAAATGACGT AACGGTTAAA GTCCACAAAA AACACCCAGA AAACCGCACG
 TTTTACTGCA TTGCCAATT CAGGTGTTTT TTGTGGGTCT TTTGGCGTGC

36251 CGAACCTACG CCCAGAAACG AAAGCCAAAA AACCCACAAC TTCCTCAAAT
 GCTTGGATGC GGGTCTTTGC TTTCGGTTTT TTGGGTGTTG AAGGAGTTTA

36301 CGTCACTTCC GTTTTCCCAC GTTACGTCAC TTCCCATTTT AAGAAACTA
 GCAGTGAAGG CAAAAGGGTG CAATGCAGTG AAGGGTAAAA TTCTTTTGAT

36351 CAATTCCCAA CACATACAAG TTAATCCGCC CTAAAACCTA CGTCAACCCG
 GTTAAGGGTT GTGTATGTTT AATGAGGCGG GATTTTGGAT GCAGTGGGCG

36401 CCCGTTCCTA CGCCCCGCGC CACGTCACAA ACTCCACCCC CTCATTATCA
 GGGCAAGGGT GCGGGGCGCG GTGCAGTGT TGAGGTGGGG GAGTAATAGT

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36451 TATTGGCTTC AATCCAAAAT AAGGTATATT ATTGATGATG TTAATTAAGA
 ATAACCGAAG TTAGGTTTTA TTCCATATAA TAACTACTAC AATTAATTCT

36501 ATTCGGATCT GCGACGCGAG GCTGGATGGC CTTCCCCATT ATGATTCTTC
 TAAGCCTAGA CGCTGCGCTC CGACCTACCG GAAGGGGTAA TACTAAGAAG

36551 TCGCTTCCGG CGGCATCGGG ATGCCCCGCT TGCAGGCCAT GCTGTCCAGG
 AGCGAAGGCC GCCGTAGCCC TACGGGCGCA ACGTCCGGTA CGACAGGTCC

36601 CAGGTAGATG ACGACCATCA GGGACAGCTT CAAGGCCAGC AAAAGGCCAG
 GTCCATCTAC TGCTGGTAGT CCCTGTCGAA GTTCCGGTCG TTTTCCGGTC

36651 GAACCGTAAA AAGGCCGCGT TGCTGGCGTT TTTCCATAGG CTCCGCCCCC
 CTTGGCATTT TTCCGGCGCA ACGACCGCAA AAAGGTATCC GAGGCGGGGG

36701 CTGACGAGCA TCACAAAAAT CGACGCTCAA GTCAGAGGTG GCGAAACCCG
 GACTGCTCGT AGTGTTTTTA GCTGCGAGTT CAGTCTCCAC CGCTTTGGGG

36751 ACAGGACTAT AAAGATACCA GGCCTTTCCC CCTGGAAGCT CCCTCGTGCG
 TGTCCTGATA TTTCTATGGT CCGCAAAGGG GGACCTTCGA GGGAGCACGC

36801 CTCTCCTGTT CCGACCCTGC CGCTTACCGG ATACCTGTCC GCCTTTCTCC
 GAGAGGACAA GGCTGGGACG GCGAATGGCC TATGGACAGG CGGAAAGAGG

36851 CTTCCGGGAAG CGTGGCGCTT TCTCATAGCT CACGCTGTAG GTATCTCAGT
 GAAGCCCTTC GCACCGCGAA AGAGTATCGA GTGCGACATC CATAGAGTCA

36901 TCGGTGTAGG TCGTTGCTC CAAGCTGGGC TGTGTGCACG AACCCCCCGT
 AGCCACATCC AGCAAGCGAG GTTCGACCCG ACACACGTGC TTGGGGGGCA

Figure 26 AM

37001	CGGTAAGACA	CGACTTATCG	CCACTGGCAG	CAGCCACTGG	TAACAGGATT
	GCCATTCTGT	GCTGAATAGC	GGTGACCGTC	GTCGGTGACC	ATTGTCTTAA
37051	AGCAGAGCGA	GGTATGTAGG	CGGTGCTACA	GAGTTCCTGA	AGTGGTGGCC
	TCGTCTCGCT	CCATACATCC	GCCACGATGT	CTCAAGAAGT	TCACCACCGG
37101	TAAC'TACGGC	TACACTAGAA	GGACAGTATT	TGGTATCTGC	GCTCTGCTGA
	ATTGATGCCG	ATGTGATCTT	CCTGTCATAA	ACCATAGACG	CGAGACGACT
37151	AGCCAGTTAC	CTTCGGAAAA	AGAGTTGGTA	GCTCTTGATC	CGGCAAAACAA
	TCGGTCAATG	GAAGCCTTTT	TCTCAACCAT	CGAGAAGTAG	GCCGTTTGT
37201	ACCACCGCTG	GTAGCGGTGG	TTTTTTTTGTT	TGCAAGCAGC	AGATTACCGG
	TGGTGGCGAC	CATCGCCACC	AAAAAAACAA	ACGTTTCGTCG	TCTAATGCGC
37251	CAGAAAAAAA	GGATCTCAAG	AAGATCCTTT	GATCTTTTCT	ACGGGGTCTG
	GTCTTTTTTT	CCTAGAGTTC	TTCTAGGAAA	CTAGAAAAGA	TGCCCCAGAC
37301	ACGCTCAGTG	GAACGAAAAC	TCACGTTAAG	GGATTTTGGT	CATGAGATTA
	TGCGAGTCAC	CTTGCTTTTG	AGTGCAATTC	CCTAAAACCA	GTACTCTAAT
37351	TCAAAAAGGA	TCTTCACCTA	GATCCTTTTA	AATCAATCTA	AAGTATATAT
	AGTTTTTCCT	AGAAGTGGAT	CTAGGAAAAT	TTAGTTAGAT	TTCATATATA
37401	GAGTAACTT	GGTCTGACAG	TTACCAATGC	TTAATCAGTG	AGGCACCTAT
	CTCATTTGAA	CCAGACTGTC	AATGGTTACG	AATTAGTCAC	TCCGTGGATA
37451	CTCAGCGATC	TGTCTATTTT	GTTTCATCCAT	AGTTGCCTGA	CTCCCCGTCG
	GAGTCGCTAG	ACAGATAAAG	CAAGTAGGTA	TCAACGGACT	GAGGGGCAGC
37501	TGTAGATAAC	TACGATACGG	GAGGGCTTAC	CATCTGGCCC	CAGTGCTGCA
	ACATCTATTG	ATGCTATGCC	CTCCCGAATG	GTAGACCGGG	GTCACGACGT
37551	ATGATACCGC	GAGACCCACG	CTCACCGGCT	CCAGATTTAT	CAGCAATAAA
	TACTATGGCG	CTCTGGGTGC	GAGTGGCCGA	GGTCTAAATA	GTCGTTATTT
37601	CCAGCCAGCC	GGAAGGGCCG	AGCGCAGAAG	TGGTCCTGCA	ACTTTATCCG
	GGTCGGTCGG	CCTTCCCGGC	TCGCGTCTTC	ACCAGGACGT	TGAAATAGGC
37651	CCTCCATCCA	GTCTATTAAT	TGTTGCCGGG	AAGCTAGAGT	AAGTAGTTCG
	GGAGGTAGGT	CAGATAATTA	ACAACGGCCC	TTGATCTCA	TTCATCAAGC
37701	CCAGTTAATA	GTTTGCGCAA	CGTTGTTGCC	ATTGCTACAG	GCATCGTGGT
	GGTCAATTAT	CAAACGCGTT	GCAACAACGG	TAACGATGTC	CGTAGCACCA
37751	GTCACGCTCG	TCGTTTGGTA	TGGCTTCATT	CAGCTCCGGT	TCCCAACGAT
	CAGTGCGAGC	AGCAAACCAT	ACCGAAGTAA	GTCGAGGCCA	AGGGTTGCTA
37801	CAAGGCGAGT	TACATGATCC	CCCATGTTGT	GCAAAAAAGC	GGTTAGCTCC
	GTTCCGCTCA	ATGTACTAGG	GGGTACAACA	CGTTTTTTTCG	CCAATCGAGG
37851	TTCGGTCCTC	CGATCGTTGT	CAGAAGTAAG	TTGGCCGCAG	TGTTATCACT
	AAGCCAGGAG	GCTAGCAACA	GTCTTCATTC	AACCGGCGTC	ACAATAGTGA

Figure 26 AN

37951 GATGCTTTTC TGTGACTGGT GAGTACTCAA CCAAGTCATT CTGAGAATAG
 CTACGAAAAG AACTGACCA CTCATGAGTT GGTTCAGTAA GACTCTTATC

 38001 TGTATGCGGC GACCGAGTTG CTCTTGCCCG GCGTCAACAC GGGATAATAC
 ACATACGCCG CTGGCTCAAC GAGAACGGGC CGCAGTTGTG CCCTATTATG

 38051 CGCGCCACAT AGCAGAACTT TAAAAGTGCT CATCATTGGA AAACGTTCTT
 GCGCGGTGTA TCGTCTTGAA ATTTTCACGA GTAGTAACCT TTTGCAAGAA

 38101 CGGGGCGAAA ACTCTCAAGG ATCTTACCGC TGTGAGATC CAGTTCGATG
 GCCCCGCTTT TGAGAGTTCC TAGAATGGCG ACAACTCTAG GTCAAGCTAC

 38151 TAACCCACTC GTGCACCCAA CTGATCTTCA GCATCTTTTA CTTTCACCAG
 ATTGGGTGAG CACGTGGGTT GACTAGAAGT CGTAGAAAAT GAAAGTGGTC

 38201 CGTTTCTGGG TGAGCAAAAA CAGGAAGGCA AAATGCCGCA AAAAAGGGAA
 GCAAAGACCC ACTCGTTTTT GTCCTTCCGT TTTACGGCGT TTTTCCCTT

 38251 TAAGGGCGAC ACGGAAATGT TGAATACTCA TACTCTTCCT TTTCAATAT
 ATTCCCGCTG TGCCTTTACA ACTTATGAGT ATGAGAAGGA AAAAGTTATA

 38301 TATTGAAGCA TTTATCAGGG TTATTGTCTC ATGAGCGGAT ACATATTTGA
 ATAACCTCGT AAATAGTCCC AATAACAGAG TACTCGCCTA TGTATAAACT

 38351 ATGTATTTAG AAAAATAAAC AAATAGGGGT TCCGCGCACA TTTCCCCGAA
 TACATAAATC TTTTATTTG TTTATCCCCA AGGCGCGTGT AAAGGGGCTT

 38401 AAGTGCCACC TGACGTCTAA GAAACCATT TATCATGAC ATTAACCTAT
 TTCACGGTGG ACTGCAGATT CTTTGGAAT AATAGTACTG TAATTGGATA

 38451 AAAAATAGGC GTATCACGAG GCCCTTTCGT CTTCAAGAAT TGGATCCGAA
 TTTTATCCG CATAGTGCTC CGGGAAAGCA GAAGTTCTTA ACCTAGGCTT

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38501 TTCTTAATTT CTTAATTAA (SEQ ID NO:32)
 AAGAATTAAA GAATTAATT (SEQ ID NO:33)

Figure 26 A0

1 CATCATCAAT AATATACCTT ATTTTGGATT GAAGCCAATA TGATAATGAG
GTAGTAGTTA TTATATGGAA TAAACCTAA CTTTCGGTTAT ACTATTACTC

51 GGGGTGGAGT TTGTGACGTG GCGCGGGGCG TGGGAACGGG GCGGGTGACG
CCCCACCTCA AACACTGCAC CGCGCCCCGC ACCCTTGCCC CGCCCACTGC

101 TAGTAGTGTG GCGGAAGTGT GATGTTGCAA GTGTGGCGGA ACACATGTAA
ATCATCACAC CGCCTTCACA CTACAACGTT CACACCGCCT TGTGTACATT

151 GCGACGGATG TGGCAAAAAGT GACGTTTTTG GTGTGCGCCG GTGTACACAG
CGCTGCCTAC ACCGTTTTCA CTGCAAAAAC CACACGCGGC CACATGTGTC

201 GAAGTGACAA TTTTCGCGCG GTTTTAGGCG GATGTTGTAG TAAATTTGGG
CTTCACTGTT AAAAGCGCGC CAAAATCCGC CTACAACATC ATTTAAACCC

251 CGTAACCGAG TAAGATTTGG CCATTTTCGC GGGAAAAC TG AATAAGAGGA
GCATTGGCTC ATTCTAAACC GGTAAAAGCG CCCTTTTGAC TTATTCTCCT

301 AGTGAAATCT GAATAATTTT GTGTTACTCA TAGCGCGTAA TATTTGTCTA
TCACTTTAGA CTTATTAAAA CACAATGAGT ATCGCGCATT ATAAACAGAT

351 GGGECGCGGG GACTTTGACC GTTTACGTGG AGACTCGCCC AGGTGTTTTT
CCCGGCGCCC CTGAAACTGG CAAATGCACC TCTGAGCGGG TCCACAAAAA

401 CTCAGGTGTT TTCCGCGTTC CGGGTCAAAG TTGGCGTTTT ATTATTATAG
GAGTCCACAA AAGGCGCAAG GCCCAGTTTC AACCGCAAAA TAATAATATC

451 GCGGCCGCGA TCCATTGCAT ACGTTGTATC CATATCATAA TATGTACATT
CGCCGGCGCT AGGTAACGTA TGCAACATAG GTATAGTATT ATACATGTAA

501 TATATTGGCT CATGTCCAAC ATTACCGCCA TGTTGACATT GATTATTGAC
ATATAACCGA GTACAGGTTG TAATGGCGGT ACAACTGTAA CTAATAACTG

551 TAGTTATTAA TAGTAATCAA TTACGGGGTC ATTAGTTCAT AGCCCATATA
ATCAATAATT ATCATTAGTT AATGCCCCAG TAATCAAGTA TCGGGTATAT

601 TGGAGTTCCG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG
ACCTCAAGGC GCAATGTATT GAATGCCATT TACCGGGCGG ACCGACTGGC

651 CCCAACGACC CCCGCCCAT TACGTCATAA ATGACGTATG TTCCCATAGT
GGGTTGCTGG GGGCGGGTAA CTGCAGTTAT TACTGCATAC AAGGGTATCA

701 AACGCCAATA GGGACTTTCC ATTGACGTCA ATGGGTGGAG TATTTACGGT
TTGCGGTTAT CCCTGAAAGG TAACTGCAGT TACCCACCTC ATAAATGCCA

751 AAAGTGGCCA CTTGGCAGTA CATCAAGTGT ATCATATGCC AAGTACGCCC
TTTGACGGGT GAACCGTCAT GTAGTTCACA TAGTATACGG TTCATGCGGG

801 CCTATTGACG TCAATGACGG TAAATGGCCC GCCTGGCATT ATGCCCAGTA
GGATAACTGC AGTTACTGCC ATTTACCGGG CGGACCGTAA TACGGGTCAT

Figure 27A

901 TCGCTATTAC CATGGTGATG CGGTTTTGGC AGTACATCAA TGGGCGTGGA
AGCGATAATG GTACCACTAC GCCAAAACCG TCATGTAGTT ACCCGCACCT

951 TAGCGGTTTG ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA
ATCGCCAAAC TGAGTGCCCC TAAAGGTTCA GAGGTGGGGT AACTGCAGTT

1001 TGGGAGTTTG TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA
ACCCTCAAAC AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT

1051 ACAACTCCGC CCCATTGACG CAAATGGGCG GTAGGCGTGT ACGGTGGGAG
TGTTGAGGCG GGGTAACTGC GTTTACCCGC CATCCGCACA TGCCACCCTC

1101 GTCTATATAA GCAGAGCTCG TTTAGTGAAC CGTCAGATCG CCTGGAGACG
CAGATATATT CGTCTCGAGC AAATCACTTG GCAGTCTAGC GGACCTCTGC

1151 CCATCCACGC TGTTTTGACC TCCATAGAAG ACACCGGGAC CGATCCAGCC
GGTAGGTGCG ACAAACCTGG AGGTATCTTC TGTGGCCCTG GCTAGGTGCG

1201 TCCGCGGCCG GGAACGGTGC ATTGGAACGC GGATTCCCCG TGCCAAGAGT
AGGCGCCGCG CTTTGCCACG TAACCTTGCG CCTAAGGGGC ACGGTTCTCA

1251 GAGATCTGCC ACCATGGCCG GCAAGTGGTC CAAGAGGTCC GTGCCCCGCT
CTCTAGACGG TGGTACCGGC CGTTCACCAG GTTCTCCAGG CACGGGCCGA

1301 GGTCCACCGT GAGGGAGAGG ATGAGGAGGG CCGAGCCCGC CGCCGACAGG
CCAGGTGGCA CTCCCTCTCC TACTCCTCCC GGCTCGGGCG GCGGCTGTCC

1351 GTGAGGAGGA CCGAGCCCGC CGCAGTGGGC GTGGGCGCCG TGTCCAGGGA
CACTCCTCCT GGCTCGGGCG GCGTCACCCG CACCCGCGGC ACAGGTCCCT

1401 CCTGGAGAAG CACGGCGCCA TCACCTCCTC CAACACCGCC GCCACCAACG
GGACCTCTTC GTGCCGCGGT AGTGGAGGAG GTTGTGGCGG CGGTGGTTGC

1451 CCGACTGCGC CTGGCTGGAG GCCCAGGAGG ACGAGGAGGT GGGCTTCCCC
GGCTGACGCG GACCGACCTC CGGGTCTCTC TGCTCTCTCA CCCGAAGGGG

1501 GTGAGGCCCC AGGTGCCCCCT GAGGCCCATG ACCTACAAGG GCGCCGTGGA
CACTCCGGGG TCCACGGGGA CTCCGGGTAC TGGATGTTCC CGCGGCACCT

1551 CCTGTCCAC TTTCTGAAGG AGAAGGGCGG CCTGGAGGGC CTGATCCACT
GGACAGGGTG AAGGACTTCC TCTTCCCGCC GGACCTCCCG GACTAGGTGA

1601 CCCAGAAGAG GCAGGACATC CTGGACCTGT GGGTGTACCA CACCCAGGGC
GGGTCTTCTC CGTCCTGTAG GACCTGGACA CCCACATGGT GTGGGTCCCG

1651 TACTTCCCCG ACTGGCAGAA CTACACCCCC GGCCCCGGCA TCAGGTTCCC
ATGAAGGGGC TGACCGTCTT GATGTGGGGG CCGGGGCCGT AGTCCAAGGG

1701 CCTGACCTTC GGCTGGTGCT TCAAGCTGGT GCCCGTGGAG CCCGAGAAGG
GGACTGGAAG CCGACCACGA AGTTCGACCA CGGGCACCTC GGGCTCTTCC

1751 TGGAGGAGGC CAACGAGGGC GAGAACAAC TCGCCGCCCA CCCCATGTCC
ACCTCCTCCG GTTGCTCCCG CTCTTGTTGA CGCGGCGGGT GGGGTACAGG

Figure 27B

1851 CTCCAAGCTG GCCTTCCACC ACGTGGCCAG GGAGCTGCAC CCCGAGTACT
GAGGTTTCGAC CGGAAGGTGG TGCACCGGTC CCTCGACGTG GGGCTCATGA

1901 ACAAGGACTG CTAAAGCCCG GGCAGATCTG CTGTGCCTTC TAGTTGCCAG
TGTTCTCTGAC GATTTTCGGG CCGTCTAGAC GACACGGAAG ATCAACGGTC

1951 CCATCTGTTG TTTGCCCTC CCCCCTGCCT TCCTTGACCC TGGGAAGGTGC
GGTAGACAAC AAACGGGGAG GGGGCACGGA AGGAAC TGGG ACCTTCCACG

2001 CACTCCCCTG GTCCTTTTCT AATAAAATGA GGAAATGCA TCGCATTTGTC
GTGAGGGTGA CAGGAAAGGA TTATTTTACT CCTTTAACGT AGCGTAACAG

2051 TGAGTAGGTG TCATTCTATT CTGGGGGGTG GGGTGGGGCA GGACAGCAAG
ACTCATCCAC AGTAAGATAA GACCCCCAC CCCACCCCGT CCTGTCGTTC

2101 GGGGAGGATT GGGGAAGACAA TAGCAGGCAT GCTGGGGATG CGGTGGGCTC
CCCCCTCTAA CCCTTCTGTT ATCGTCCGTA CGACCCCTAC GCCACCCGAG

2151 TATGGCCGAT CGGCGCGCCG TACTGAAATG TGTGGGCGTG GCTTAAGGGT
ATACCGGCTA GCCGCGCGGC ATGACTTTAC ACACCCGCAC CGAATTCCCA

2201 GGGAAAGAAT ATATAAGGTG GGGGTCTTAT GTAGTTTTGT ATCTGTTTTG
CCCTTTCTTA TATATTCCAC CCCCAGAATA CATCAAAACA TAGACAAAAC

2251 CAGCAGCCGC CGCCGCCATG AGCACCAACT CGTTTGATGG AAGCATTTGTC
GTCGTCGGCG GCGGCGGTAC TCGTGGTTGA GCAAAC TACC TTCGTAACAC

2301 AGCTCATATT TGACAACGCG CATGCCCCCA TGGGCCGGGG TGCCTCAGAA
TCGAGTATAA ACTGTTGCGC GTACGGGGGT ACCCGGCCCC ACGCAGTCTT

2351 TGTGATGGGC TCCAGCATTG ATGGTCGCCC CGTCCTGCCC GCAAAC TCTA
ACACTACCCG AGGTCGTAAC TACCAGCGGG GCAGGACGGG CGTTTGAGAT

2401 CTACCTTGAC CTACGAGACC GTGTCTGGAA CGCCGTTGGA GACTGCAGCC
GATGGAAC TG GATGCTCTGG CACAGACCTT GCGGCAACCT CTGACGTCGG

2451 TCCGCCGCCG CTTAGCCGC TGCAGCCACC GCCCGCGGGA TTGTGACTGA
AGGCGGCGGC GAAGTCGGCG ACGTCGGTGG CGGGCGCCCT AACACTGACT

2501 CTTTGCTTTC CTGAGCCCGC TTGCAAACAG TGCAGCTTCC CGTTCATCCG
GAAACGAAAG GACTCGGGCG AACGTTTGTC ACGTCGAAGG GCAAGTAGGC

2551 CCCGCGATGA CAAGTTGACG GCTCTTTTGG CACAATTGGA TTCTTTGACC
GGGCGCTACT GTTCAACTGC CGAGAAAACC GTGTTAACCT AAGAACTGG

2601 CGGGAACCTA ATGTCGTTTC TCAGCAGCTG TTGGATCTGC GCCAGCAGGT
GCCCTTGAAT TACAGCAAAG AGTCGTCGAC AACCTAGACG CGGTCGTCCA

2651 TTCTGCCCTG AAGGCTTCCT CCCCTCCCAA TGCGGTTTAA AACATAAATA
AAGACGGGAC TTCCGAAGGA GGGGAGGGTT ACGCCAAAT TTGTATTTAT

2701 AAAAACCAGA CTCTGTTTGG ATTTGGATCA AGCAAGTGTC TTGCTGTCTT
TTTTTGGTCT GAGACAAACC TAAACCTAGT TCGTTCACAG AACGACAGAA

Figure 27C

2751	TATTTAGGGG	TTTTGCGCGC	GCGGTAGGCC	CGGGACCA	GGTCTCGGTC
	ATAAATCCCC	AAAACGCGCG	CGCCATCCGG	GCCCTGGTCG	CCAGAGCCAG
2801	GTTGAGGGTC	CTGTGTATTT	TTTCCAGGAC	GTGGTAAAGG	TGACTCTGGA
	CAACTCCCAG	GACACATAAA	AAAGGTCCTG	CACCATTTC	ACTGAGACCT
2851	TGTTCAAGATA	CATGGGCATA	AGCCCGTCTC	TGGGGTGGAG	GTAGCACCAC
	ACAAGTCTAT	GTACCCGTAT	TCGGGCAGAG	ACCCACCTC	CATCGTGGTG
2901	TGCAGAGCTT	CATGCTGCGG	GGTGGTGTG	TAGATGATCC	AGTCGTAGCA
	ACGTCTCGAA	GTACGACGCC	CCACCACAAC	ATCTACTAGG	TCAGCATCGT
2951	GGAGCGCTGG	GCGTGGTGCC	TAAAAATGTC	TTTCAGTAGC	AAGCTGATTG
	CTCTCGGACC	CGCACCACGG	ATTTTACAG	AAAGTCATCG	TTCGACTAAC
3001	CCAGGGGCAG	GCCCTTGGTG	TAAGTGTTTA	CAAAGCGGTT	AAGCTGGGAT
	GGTCCCCGTC	CGGGAACCAC	ATTCACAAAT	GTTTCGCCAA	TTCGACCCTA
3051	GGGTGCATAC	GTGGGGATAT	GAGATGCATC	TTGGACTGTA	TTTTTAGGTT
	CCCACGTATG	CACCCCTATA	CTCTACGTAG	AACCTGACAT	AAAAATCCAA
3101	GGCTATGTTT	CCAGCCATAT	CCCTCCGGGG	ATTCATGTTG	TGCAGAACCA
	CCGATACAAG	GGTCGGTATA	GGGAGGCCCC	TAAGTACAAC	ACGTCTTGGT
3151	CCAGCACAGT	GTATCCGGTG	CACTTGGGAA	ATTTGTCATG	TAGCTTAGAA
	GGTCGTGTCA	CATAGGCCAC	GTGAACCCTT	TAAACAGTAC	ATCGAATCTT
3201	GGAAATGCGT	GGAAGAACTT	GGAGACGCCC	TTGTGACCTC	CAAGATTTTC
	CCTTTACGCA	CCTTCTTGAA	CCTCTGCGGG	AACACTGGAG	GTTCTAAAAG
3251	CATGCATTCT	TCCATAATGA	TGGCAATGGG	CCCACGGGCG	GCGGCCTGGG
	GTACGTAAGC	AGGTATTACT	ACCGTTACCC	GGGTGCCCGC	CGCCGGACCC
3301	CGAAGATATT	TCTGGGATCA	CTAACGTCAT	AGTTGTGTTC	CAGGATGAGA
	GCTTCTATAA	AGACCCTAGT	GATTGCAGTA	TCAACACAAG	GTCTACTCT
3351	TCGTCATAGG	CCATTTTTTAC	AAAGCGCGGG	CGGAGGGTGC	CAGACTGCGG
	AGCAGTATCC	GGTAAAAATG	TTTCGCGCCC	GCTTCCACG	GTCTGACGCC
3401	TATAATGGTT	CCATCCGGCC	CAGGGGCGTA	GTTACCCTCA	CAGATTTGCA
	ATATTACCAA	GGTAGGCCGG	GTCCCCGCAT	CAATGGGAGT	GTCTAAACGT
3451	TTTCCCACGC	TTTGAGTTCA	GATGGGGGGA	TCATGTCTAC	CTGCGGGGCG
	AAAGGGTGCG	AAACTCAAGT	CTACCCCCCT	AGTACAGATG	GACGCCCCCG
3501	ATGAAGAAAA	CGGTTTCCGG	GGTAGGGGAG	ATCAGCTGGG	AAGAAAGCAG
	TACTTCTTTT	GCCAAAGGCC	CCATCCCCTC	TAGTCGACCC	TTCTTTTCGTC
3551	GTTCTTGAGC	AGCTGCGACT	TACCGCAGCC	GGTGGGCCCC	TAAATCACAC
	CAAGGACTCG	TCGACGCTGA	ATGGCGTCGG	CCACCCGGGC	ATTTAGTGTG
3601	CTATTACCGG	CTGCAACTGG	TAGTTAAGAG	AGCTGCAGCT	GCCGTCATCC
	GATAATGGCC	GACGTTGACC	ATCAATTCTC	TCGACGTCTG	CGGCAGTAGG
3651	CTGAGCAGGG	GGGCCACTTC	GTAAAGCATG	TCCCTGACTC	GCATGTTTTT
	GACTCGTCCC	CCCGGTGAAG	CAATTCTGAC	AGGGACTGAG	CGTACAAAAG

3701 CCTGACCAAA TCCGCCAGAA GGCGCTCGCC GCCCAGCGAT AGCAGTTCTT
GGACTGGTTT AGGCGGTCTT CCGCAGCGG CGGGTCGCTA TCGTCAAGAA

3751 GCAAGGAAGC AAAGTTTTTC AACGGTTTGA GACCGTCCGC CGTAGGCATG
CGTTCCTTCG TTTCAAAAAG TTGCCAAACT CTGGCAGGCG GCATCCGTAC

3801 CTTTTGAGCG TTTGACCAAG CAGTTCAGG CGGTCCCACA GCTCGGTCAC
GAAAACTCGC AAACCTGGTTC GTCAAGGTCC GCCAGGGTGT CGAGCCAGTG

3851 CTGCTCTACG GCATCTCGAT CCAGCATATC TCCTCGTTTC GCGGGTTGGG
GACGAGATGC CGTAGAGCTA GGTCTGTATAG AGGAGCAAAG CGCCCAACCC

3901 GCGGCTTTTCG CTGTACGGCA GTAGTCGGTG CTCGTCCAGA CGGGCCAGGG
CGCCGAAAGC GACATGCCGT CATCAGCCAC GAGCAGGTCT GCCCGGTCCC

3951 TCATGTCTTT CCACGGGCGC AGGGTCCTCG TCAGCGTAGT CTGGGTCACG
AGTACAGAAA GGTGCCCGCG TCCCAGGAGC AGTCGCATCA GACCCAGTGC

4001 GTGAAGGGGT GCGCTCCGGG CTGCGCGCTG GCCAGGGTGC GCTTGAGGCT
CACTTCCCCA CGCGAGGCCG GACGCGCGAC CGGTCCCACG CGAACTCCGA

4051 GGTCTCTGCTG GTGCTGAAGC GCTGCCGGTC TTCGCCCTGC GCGTCGGCCA
CCAGGACGAC CACGACTTCG CGACGGCCAG AAGCGGGACG CGCAGCCGGT

4101 GGTAGCATTT GACCATGGTG TCATAGTCCA GCCCCTCCGC GCGGTGGCCC
CCATCGTAAA CTGGTACCAC AGTATCAGGT CGGGGAGGCG CCGCACCGGG

4151 TTGGCGCGCA GCTTGCCCTT GGAGGAGGCG CCGCACGAGG GGCAGTGCAG
AACC GC GCGT CGAACGGGAA CCTCCTCCGC GCGTGCTCC CCGTCACGTC

4201 ACTTTTGAGG GCGTAGAGCT TGGGCGCGAG AAATACCGAT TCCGGGGAGT
TGAAAACCTC CGCATCTCGA ACCCGCGCTC TTTATGGCTA AGGCCCTCA

4251 AGGCATCCGC GCCGCAGGCC CCGCAGACGG TCTCGCATTC CACGAGCCAG
TCCGTAGGCG CGGCGTCCGG GCGTCTGCC AGAGCGTAAG GTGCTCGGTC

4301 GTGAGCTCTG GCCGTTTCGGG GTCAAAAACC AGGTTTCCCC CATGCTTTTT
CACTCGAGAC CGGCAAGCCC CAGTTTTTGG TCCAAAGGGG GTACGAAAAA

4351 GATGCGTTTC TTACCTCTGG TTTCCATGAG CCGGTGTCCA CGCTCGGTGA
CTACGCAAAG AATGGAGACC AAAGGTACTC GGCCACAGGT GCGAGCCACT

4401 CGAAAAGGCT GTCCGTGTCC CCGTATACAG ACTTGAGAGG CCTGTCTCTG
GCTTTTCCGA CAGGCACAGG GGCATATGTC TGAACCTCTC GGACAGGAGC

4451 AGCGGTGTTTC CGCGGTCTCT CTCGTATAGA AACTCGGACC ACTCTGAGAC
TCGCCACAAG GCGCCAGGAG GAGCATATCT TTGAGCCTGG TGAGACTCTG

4501 AAAGGCTCGC GTCCAGGCCA GCACGAAGGA GGCTAAGTGG GAGGGGTAGC
TTTCCGAGCG CAGGTCCGGT CGTGCTTCCT CCGATTACAC CTCCCCATCG

4551 GGTGCTTGTC CACTAGGGGG TCCACTCGCT CCAGGGTGTG AAGACACATG
CCAGCAACAG GTGATCCCC AGGTGAGCGA GGTCCACAC TTCTGTGTAC

4601 TCGCCCTCTT CGGCATCAAG GAAGGTGATT GGTGTGTAGG TGTAGGCCAC
AGCGGGAGAA GCCGTAGTTC CTTCCACTAA CCAAACATCC ACATCCGGTG

Figure 27E

4701 CGTCCTCACT CTCCTCCGCA TCGCTGTCTG CGAGGGCCAG CTGTTGGGGT
GCAGGAGTGA GAGAAGGCGT AGCGACAGAC GCTCCCGGTC GACAACCCCA

4751 GAGTACTCCC TCTGAAAAGC GGGCATGACT TCTGCGCTAA GATTGTGAGT
CTCATGAGGG AGACTTTTTCG CCCGTACTGA AGACGCGATT CTAACAGTCA

4801 TTCCAAAAAC GAGGAGGATT TGATATTAC CTTGGCCCGC GTGATGCCTT
AAGGTTTTTG CTCCTCCTAA ACTATAAGTG GACCGGGCGC CACTACGGAA

4851 TGAGGGTGGC CGCATCCATC TGGTCAGAAA AGACAATCTT TTTGTTGTCA
ACTCCCACCG GCGTAGGTAG ACCAGTCTTT TCTGTTAGAA AAACAACAGT

4901 AGCTTGGTGG CAAACGACCC GTAGAGGGCG TTGGACAGCA ACTTGCGCAT
TCGAACCACC GTTTGCTGGG CATCTCCCGC AACCTGTCGT TGAACCGCTA

4951 GGAGCGCAGG GTTTGGTTTT TGTCGCGATC GCGCGCTCC TTGGCCGCGA
CCTCGCGTCC CAAACCAAAA ACAGCGCTAG CCGCGCGAGG AACCGGCGCT

5001 TGTTTAGCTG CACGTATTCG CGCGCAACGC ACCGCCATTC GGGAAAGACG
ACAAATCGAC GTGCATAAGC GCGCGTTGCG TGGCGGTAAG CCTTTCTGC

5051 GTGGTGCCTG CGTCGGGCAC CAGGTGCACG CGCCAACCGC GGTGTGTGAG
CACCACGCGA GCAGCCCGTG GTCCACGTGC GCGGTTGGCG CCAACACGTC

5101 GGTGACAAGG TCAACGCTGG TGGCTACCTC TCCGCGTAGG CGCTCGTTGG
CCACTGTTCC AGTTGCGACC ACCGATGGAG AGGCGCATCC GCGAGCAACC

5151 TCCAGCAGAG GCGGCCGCCC TTGCGCGAGC AGAATGGCGG TAGGGGGTCT
AGGTCGTCTC CGCCGGCGGG AACGCGCTCG TCTTACCGCC ATCCCCCAGA

5201 AGCTGCGTCT CGTCCGGGGG GTCTGCGTCC ACGGTAAAGA CCCCAGGAG
TCGACGCAGA GCAGGCCCCC CAGACGCAGG TGCCATTCTT GGGGCCCGTC

5251 CAGGCGCGCG TCGAAGTAGT CTATCTTGCA TCCTTGCAAG TCTAGCGCCT
GTCCGCGCGC AGCTTCATCA GATAGAACGT AGGAACGTTT AGATCGCGGA

5301 GCTGCCATGC GCGGGCGGCA AGCGCGCGCT CGTATGGGTT GAGTGGGGGA
CGACGGTACG CGCCCGCCGT TCGCGCGCGA GCATACCCAA CTCACCCCTT

5351 CCCCATGGCA TGGGGTGGGT GAGCGCGGAG GCGTACATGC CGCAAATGTC
GGGGTACCGT ACCCCACCCA CTCGCGCCTC CGCATGTACG GCGTTTACAG

5401 GTAAACGTAG AGGGGCTCTC TGAGTATTCC AAGATATGTA GGGTAGCATC
CATTTGCATC TCCCCGAGAG ACTCATAAGG TTCTATACAT CCCATCGTAG

5451 TTCCACCGCG GATGCTGGCG CGCACGTAAT CGTATAGTTC GTGCGAGGGA
AAGGTGGCGC CTACGACCGC GCGTGCAATTA GCATATCAAG CACGCTCCCT

5501 GCGAGGAGGT CGGGACCGAG GTTGCTACGG GCGGGCTGCT CTGCTCGGAA
CGCTCTCCA GCCCTGGCTC CAACGATGCC CGCCCGACGA GACGAGCCTT

5551 GACTATCTGC CTGAAGATGG CATGTGAGTT GGATGATATG GTTGGACGCT
CTGATAGACG GACTTCTACC GTACACTCAA CCTACTATAC CAACCTGCGA

Figure 27F

5651 GAGGCGTAGG AGTCGCGCAG CTTGTTGACC AGCTCGGCGG TGACCTGCAC
CTCCGCATCC TCAGCGCGTC GAACAACTGG TCGAGCCGCC ACTGGACGTG

5701 GTCTAGGGCG CAGTAGTCCA GGGTTTCCTT GATGATGTCA TACTTATCCT
CAGATCCCCG GTCATCAGGT CCCAAAGGAA CTACTACAGT ATGAATAGGA

5751 GTCCCTTTTT TTTCCACAGC TCGCGGTTGA GGACAACTC TTCGCGGTCT
CAGGGAAAAA AAAGGTGTCG AGCGCCAACT CCTGTTTGAG AAGCGCCAGA

5801 TTCCAGTACT CTTGGATCGG AAACCCGTCG GCCTCCGAAC GGTAAGAGCC
AAGGTCATGA GAACCTAGCC TTTGGGCAGC CGGAGGCTTG CCATTCTCGG

5851 TAGCATGTAG AACTGGTTGA CGGCCTGGTA GGCGCAGCAT CCCTTTTCTA
ATCGTACATC TTGACCAACT GCCGGACCAT CCGCGTCGTA GGGAAAAGAT

5901 CGGGTAGCGC GTATGCCCTGC GCGGCCCTTCC GGAGCGAGGT GTGGGTGAGC
GCCCATCGCG CATACGGACG CGCCGGAAGG CCTCGCTCCA CACCCACTCG

5951 GCAAAGGTGT CCCTGACCAT GACTTTGAGG TACTGGTATT TGAAGTCAGT
CGTTTCCACA GGGACTGGTA CTGAACTCC ATGACCATAA ACTTCAGTCA

6001 GTCGTCGCAT CCGCCCTGCT CCCAGAGCAA AAAGTCCGTG CGCTTTTGG
CAGCAGCGTA GCGGGGACGA GGGTCTCGTT TTTCAGGCAC GCGAAAACC

6051 AACGCGGATT TGGCAGGGCG AAGGTGACAT CGTTGAAGAG TATCTTTCCC
TTGCGCCTAA ACCGTCCCGC TTCCACTGTA GCAACTTCTC ATAGAAAGGG

6101 GCGCGAGGCA TAAAGTTGCG TGTGATGCGG AAGGGTCCCG GCACCTCGGA
CGCGCTCCGT ATTTCAACGC AACTACGCC TTCCCAGGGC CGTGGAGCCT

6151 ACGGTTGTTA ATTACCTGGG CGGCGAGCAC GATCTCGTCA AAGCCGTTGA
TGCCAACAAT TAATGGACCC GCCGCTCGTG CTAGAGCAGT TTCGGCAACT

6201 TGTTGTGGCC CACAATGTAA AGTTCCAAGA AGCGCGGGAT GCCCTTGATG
ACAACACCGG GTGTTACATT TCAAGGTTCT TCGCGCCCTA CGGGAACCTAC

6251 GAAGGCAATT TTTTAAGTTC CTCGTAGGTG AGCTCTTCAG GGGAGCTGAG
CTTLCGTAA AAAATTCAAG GAGCATCCAC TCGAGAAGTC CCCTCGACTC

6301 CCCGTGCTCT GAAAGGGCCC AGTCTGCAAG ATGAGGGTTG GAAGCGACGA
GGGCACGAGA CTTTCCCGGG TCAGACGTTT TACTCCCAAC CTTGCTGCT

6351 ATGAGCTCCA CAGGTCACGG GCCATTAGCA TTTGCAGGTG GTCGCGAAAG
TACTCGAGGT GTCCAGTGCC CGGTAATCGT AAACGTCCAC CAGCGCTTTC

6401 GTCCTAAACT GGCGACCTAT GGCCATTTTT TCTGGGGTGA TGCAGTAGAA
CAGGATTTGA CCGCTGGATA CCGGTAAAAA AGACCCCACT ACGTCTCTT

6451 GGTAAGCGGG TCTTGTTCCC AGCGGTCCCA TCCAAGGTTT GCGGCTAGGT
CCATTGCCCC AGAACAAGGG TCGCCAGGGT AGGTTCCAAG CGCCGATCCA

6501 CTCGCGCGGC AGTCACTAGA GGCTCATCTC CGCCGAACCT CATGACCAGC
GAGCGCGCCG TCAGTGATCT CCGAGTAGAG GCGGCTTGAA GTACTGGTGC

Figure 27G

6601 TACATCGTAG GTGACAAAGA GACGCTCGGT GCGAGGATGC GAGCCGATCG
 ATGTAGCATC CACTGTTTCT CTGCGAGCCA CGCTCCTACG CTCGGCTAGC

6651 GGAAGAACTG GATCTCCCGC CACCAATTGG AGGAGTGGCT ATTGATGTGG
 CCTTCTTGAC CTAGAGGGCG GTGGTTAACC TCCTCACCAG TAACTACACC

6701 TGAAAGTAGA AGTCCCTGCG ACGGGCCGAA CACTCGTGCT GGCTTTTGTA
 ACTTTCATCT TCAGGGACGC TGCCCGGCTT GTGAGCACGA CCGAAAACAT

6751 AAAACGTGCG CAGTACTGGC AGCGGTGCAC GGGCTGTACA TCCTGCACGA
 TTTTGACACG GTCATGACCG TCGCCACGTG CCCGACATGT AGGACGTGCT

6801 GGTGACCTG ACGACCGCGC ACAAGGAAGC AGAGTGGGAA TTTGAGCCCC
 CCAACTGGAC TGCTGGCGCG GTTTCCTTCG TCTCACCCTT AAACTCGGGG

6851 TCGCCTGGCG GGTTCGGCTG GTGGTCTTCT ACTTCGGCTG CTTGTCTTG
 AGCGGACCGC CCAAACCGAC CACCAGAAGA TGAAGCCGAC GAACAGGAAC

6901 ACCGTCTGGC TGCTCGAGGG GAGTTACGGT GGATCGGACC ACCACGCCGC
 TGGCAGACCG ACGAGCTCCC CTCAATGCCA CCTAGCCTCG TGGTGCGGCG

6951 GCGAGCCCAA AGTCCAGATG TCCGCGCGCG GCGGTCCGAG CTTGATGACA
 CGCTCGGGTT TCAGGTCTAC AGGCGCGCGC CGCCAGCCTC GAACTACTGT

7001 ACATCGCGCA GATGGGAGCT GTCCATGGTC TGGAGCTCCC GCGGCGTCAG
 TGTCGCGCT CTACCCTCGA CAGGTACCAG ACCTCGAGGG CGCCGCAGTC

7051 GTCAGGCGGG AGCTCCTGCA GGTTTACCTC GCATAGACGG GTCAGGGCGC
 CAGTCCGCCC TCGAGGACGT CCAAATGGAG CGTATCTGCC CAGTCCCGCG

7101 GGGCTAGATC CAGGTGATAC CTAATTTCCA GGGGCTGGTT GGTGGCGGCG
 CCCGATCTAG GTCCACTATG GATTAAAGGT CCCCAGCCAA CCACCGCCGC

7151 TCGATGGCTT GCAAGAGGCC GCATCCCCGC GGC GCGACTA CGGTACCGCG
 AGCTACCGAA CGTTCCTCCG CGTAGGGGCG CCGCGCTGAT GCCATGGCGC

7201 CGGCGGGCGG TGGGCCGCGG GGGTGTCTT GGATGATGCA TCTAAAAGCG
 GCCGCCCGCC ACCCGGCGCC CCCACAGGAA CCTACTACGT AGATTTTCGC

7251 GTGACGCGGG CGAGCCCCCG GAGGTAGGGG GGGCTCCGGA CCCGCCGGGA
 CACTGCGCCC GCTCGGGGGC CTCCATCCCC CCCGAGGCCT GGGCGGCCCT

7301 GAGGGGGCAG GGGCACGTCG GCGCCGCGCG CGGGCAGGAG CTGGTGCTGC
 CTCCCCCGTC CCCGTGCAGC CGCGGCGCGC GCCCGTCCTC GACCACGACG

7351 GCGCGTAGGT TGCTGGCGAA CGCGACGACG CGGCGGTTGA TCTCCTGAAT
 CGCGCATCCA ACGACCGCTT GCGCTGCTGC GCCGCCAACT AGAGGACTTA

7401 CTGGCGCCTC TGCGTGAAGA CGACGGGCCC GGTGAGCTTG AACCTGAAAG
 GACCGCGGAG ACGCACTTCT GCTGCCCCGG CCACTCGAAC TTGGACTTTC

7451 AGAGTTCGAC AGAATCAATT TCGGTGTCGT TGACGGCGGC CTGGCGCAAA
 TCTCAAGCTG TCTTAGTTAA AGCCACAGCA ACTGCCGCCG GACCGCGTTT

Figure 27H

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7551 CTGCTCGATC TCTTCTCCTT GGAGATCTCC GCGTCCGGCT CGCTCCACGG
      GACGAGCTAG AGAAGGAGGA CCTCTAGAGG CGCAGGCCGA GCGAGGTGCC

7601 TGGCGGCGAG GTCGTTGGAA ATGCGGGCCA TGAGCTGCGA GAAGGCGTTG
      ACCGCCGCTC CAGCAACCTT TACGCCCCGT ACTCGACGCT CTTCCGCAAC

7651 AGGCCCTCCCT CGTTCCAGAC GCGGCTGTAG ACCACGCCCC CTTCCGGCATC
      TCCGGAGGGA GCAAGGTCTG CGCCGACATC TGGTGCGGGG GAAGCCGTAG

7701 GCGGGCGCGC ATGACCACCT GCGCGAGATT GAGCTCCACG TGCCGGGCGA
      CGCCCGCGCG TACTGGTGGA CGCGCTCTAA CTCGAGGTGC ACGGCCCGCT

7751 AGACGGCGTA GTTTCGCAGG CGCTGAAAGA GGTAGTTGAG GGTGGTGCGG
      TCTGCCGCAT CAAAGCGTCC GCGACTTTCT CCATCAACTC CCACCACCGC

7801 GTGTGTTCTG CCACGAAGAA GTACATAACC CAGCGTCGCA ACGTGGATTTC
      CACACAAGAC GGTGCTTCTT CATGTATTGG GTCGCAGCGT TGCACCTAAG

7851 GTTGATATCC CCCAAGGCCT CAAGGCGCTC CATGGCCTCG TAGAAGTCCA
      CAACTATAGG GGGTTCCGGA GTTCCGCGAG GTACCGGAGC ATCTTCAGGT

7901 CGGCGAAGTT GAAAAACTGG GAGTTGCGCG CCGACACGGT TAACTCCTCC
      GCCGCTTCAA CTTTTTGACC CTCAACGCGC GGCTGTGCCA ATTGAGGAGG

7951 TCCAGAAGAC GGATGAGCTC GGCACAGTG TCGCGCACCT CGCGCTCAAA
      AGGTCTTCTG CCTACTCGAG CCGCTGTCAC AGCGCGTGGA GCGCGAGTTT

8001 GGCTACAGGG GCCTCTTCTT CTTCTTCAAT CTCCTCTTCC ATAAGGGCCT
      CCGATGTCCC CGGAGAAGAA GAAGAAGTTA GAGGAGAAGG TATTCGCCGA

8051 CCCCTTCTTC TTCTTCTGGC GCGGGTGGGG GAGGGGGGAC ACGGCGGCGA
      GGGGAAGAAG AAGAAGACCG CCGCCACCCC CTCCCCCTG TGCCGCCGCT

8101 CGACGGCGCA CCGGGAGGCG GTCGACAAAG CGCTCGATCA TCTCCCCGCG
      GCTGCCGCGT GGCCCTCCGC CAGCTGTTTC GCGAGCTAGT AGAGGGGCGC

8151 GCGACGGCGC ATGGTCTCGG TGACGGCGCG GCCGTTCTCG CGGGGGCGCA
      CGTGCCGCG TACCAGAGCC ACTGCCGCGC CGGCAAGAGC GCGCCGCGT

8201 GTTGGAAGAC GCCGCCGTC ATGTCCCGGT TATGGGTTGG CGGGGGGCTG
      CAACCTTCTG CGGCGGGCAG TACAGGGCCA ATACCAACC GCGCCCGAC

8251 CCATGCGGCA GGGATACGGC GCTAACGATG CATCTCAACA ATTGTTGTGT
      GGTACGCCGT CCTATGCCG CGATTGCTAC GTAGAGTTGT TAACAACACA

8301 AGGTACTCCG CCGCCGAGGG ACCTGAGCGA GTCCGCATCG ACCGGATCGG
      TCCATGAGGC GCGGCTCCC TGGACTCGCT CAGGCGTAGC TGGCCTAGCC

8351 AAAACCTCTC GAGAAAGGCG TCTAACCAGT CACAGTCGCA AGGTAGGCTG
      TTTTGGAGAG CTCTTTCCGC AGATTGGTCA GTGTCAGCGT TCCATCCGAC

8401 AGCACCGTGG CGGGCGGCAG CGGGCGGCGG TCGGGGTTGT TTCTGGCGGA
      TCGTGGCACC GCGCGCCGTC GCGCGCCGCC AGCCCCAACA AAGACCGCCT

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Figure 27I

8501 TCGACAGAAG CACCATGTCC TTGGGTCCGG CCTGCTGAAT GCGCAGGCGG
 AGCTGTCTTC GTGGTACAGG AACCCAGGCC GGACGACTTA CGCGTCCGCG

8551 TCGGCCATGC CCCAGGCTTC GTTTTGACAT CGGCGCAGGT CTTTGTAAGTA
 AGCCGGTACG GGGTCCGAAG CAAAACGTGA GCCGCGTCCA GAAACATCAT

8601 GTCTTGCAATG AGCCTTTCTA CCGGCACTTC TTCTTCTCCT TCCTCTTGTC
 CAGAACGTAC TCGGAAAGAT GGCCGTGAAG AAGAAGAGGA AGGAGAACAG

8651 CTGCATCTCT TGCACTATATC GCTGCGGCGG CGGCGGAGTT TGGCCGTAGG
 GACGTAGAGA ACGTAGATAG CGACGCCGCC GCCGCCTCAA ACCGGCATCC

8701 TGGCGCCCTC TTCCTCCCAT GCGTGTGACC CCGAAGCCCC TCATCGGCTG
 ACCGCGGGAG AAGGAGGGTA CGCACACTGG GGCTTCGGGG AGTAGCCGAC

8751 AAGCAGGGCT AGGTCCGGCA CAACGCGCTC GGCTAATATG GCCTGCTGCA
 TTCGTCCGA TCCAGCCGCT GTTGCGCGAG CCGATTATAC CGGACGACGT

8801 CCTGCGTGAG GGTAGACTGG AAGTCATCCA TGTCCACAAA GCGGTGGTAT
 GGACGCACTC CCATCTGACC TTCAGTAGGT ACAGGTGTTT CGCCACCATA

8851 GCGCCCGTGT TGATGGTGTA AGTGCAGTTG GCCATAACGG ACCAGTTAAC
 CGCGGGCACA ACTACCACAT TCACGTCAAC CGGTATTGCC TGGTCAATTG

8901 GGTCTGGTGA CCCGGCTGCG AGAGCTCGGT GTACCTGAGA CGCGAGTAAG
 CCAGACCACT GGGCCGACGC TCTCGAGCCA CATGGACTCT GCGCTCATTC

8951 CCCTCGAGTC AAATACGTAG TCGTTGCAAG TCCGCACCAG GTACTGGTAT
 GGGAGCTCAG TTTATGCATC AGCAACGTTT AGGCGTGGTC CATGACCATA

9001 CCCACCAAAA AGTGCGGCGG CGGCTGGCGG TAGAGGGGCC AGCGTAGGGT
 GGGTGGTTTT TCACGCCGCC GCCGACGCC ATCTCCCCCG TCGCATCCCA

9051 GGCCGGGGCT CCGGGGGCGA GATCTTCCAA CATAAGGCGA TGATATCCGT
 CCGGCCCCGA GGCCCCCGCT CTAGAAGGTT GTATTCCGCT ACTATAGGCA

9101 AGATGTACCT GGACATCCAG GTGATGCCGG CGGCGGTGGT GGAGGCGCGC
 TCTACATGGA CCTGTAGGTC CACTACGCC GCCGCCACCA CCTCCGCGCG

9151 GGAAAGTCGC GGACGCGGTT CCAGATGTTG CGCAGCGGCA AAAAGTGCTC
 CCTTTCAGCG CCTGCGCCAA GGTCTACAAC GCGTCGCCGT TTTTCACGAG

9201 CATGGTCGGG ACGCTCTGGC CGGTCAGGCG CGCGCAATCG TTGACGCTCT
 GTACCAGCCC TGCAGAGCCG GCCAGTCCGC GCGCGTTAGC AACTGCGAGA

9251 AGACCGTGCA AAAGGAGAGC CTGTAAGCGG GCACTCTTCC GTGGTCTGGT
 TCTGGCACGT TTTCTCTCG GACATTGCCC CGTGAGAAGG CACCAGACCA

9301 GGATAAATTC GCAAGGGTAT CATGGCGGAC GACCGGGGTT CGAGCCCCGT
 CCTATTAAAG CGTTCCATA GTACCGCCTG CTGGCCCCAA GCTCGGGGCA

9351 ATCCGGCCGT CCGCCGTGAT CCATGCGGTT ACCGCCCGCG TGTGCAACCC
 TAGGCGGGCA GCGGGCACTA GGTACGCCAA TGGCGGGCGC ACAGCTTGGG

Figure 27J

9451 GGC GCGGCGG CTGCTGCGCT AGCTTTTTTTG GCCACTGGCC GCGCGCAGCG
 CCGCGCCGCC GACGACGCGA TCGAAAAAAC CGGTGACCGG CCGCGCTCGC
 9501 TAAGCGGT TA GGCTGGAAAG CGAAAGCATT AAGTGGCTCG CTCCCTGTAG
 ATTCGCCAAT CCGACCTTTC GCTTTCGTAA TTCACCGAGC GAGGGACATC
 9551 CCGGAGGGTT ATTTTCCAAG GGTGAGTCG CGGGACCCCC GGTTCGAGTC
 GGCTTCCCAA TAAAAGGTTT CCAACTCAGC GCCCTGGGGG CCAAGCTCAG
 9601 TCGGACCGGC CGGACTGCGG CGAACGGGGG TTTGCCTCCC CGTCATGCAA
 AGCCTGGCCG GCCTGACGCC GCTTGCCCCC AAACGGAGGG GCAGTACGTT
 9651 GACCCCGCTT GCAAATTCCT CCGGAAACAG GGACGAGCCC CTTTTTTGCT
 CTGGGGCGAA CGTTTAAGGA GGCTTTTGTC CCTGCTCGGG GAAAAAACGA
 9701 TTTCCAGAT GCATCCGGTG CTGCGGCAGA TGCGCCCCC TCCTCAGCAG
 AAAGGGTCTA CGTAGGCCAC GACGCCGTCT ACGCGGGGGG AGGAGTCGTC
 9751 CGGCAAGAGC AAGAGCAGCG GCAGACATGC AGGGCACCCCT CCCCTCCTCC
 GCCGTTCTCG TTCTCGTCGC CGTCTGTACG TCCCGTGGGA GGGGAGGAGG
 9801 TACCGCGTCA GGAGGGGCGA CATCCGCGGT TGACGCGGCA GCAGATGGTG
 ATGGCGCAGT CCTCCCCGCT GTAGGCGCCA ACTGCGCCGT CGTCTACCAC
 9851 ATTACGAACC CCCGCGGCGC CGGGCCCCGGC ACTACCTGGA CTTGGAGGAG
 TAATGCTTGG GGGCGCCGCG GCCCGGGCCG TGATGGACCT GAACCTCCTC
 9901 GGCAGAGGCC TGGCGCGGCT AGGAGCGCCC TCTCCTGAGC GGCACCCAAG
 CCGCTCCCGG ACCGCGCCGA TCCTCGCGGG AGAGGACTCG CCGTGGGTTC
 9951 GGTGCAGCTG AAGCGTGATA CGCGTGAGGC GTACGTGCCG CGGCAGAACC
 CCACGTCGAC TTCGCACTAT GCGCACTCCG CATGCACGGC GCCGTCTTGG
 10001 TGTTTTCGCA CCGCGAGGGA GAGGAGCCCC AGGAGATGCG GGATCGAAAG
 ACAAAGCGCT GCGCTCCCT CTCTCGGGC TCCTCTACGC CCTAGCTTTC
 10051 TTCCACGCAG GCGCGAGCT GCGGCATGGC CTGAATCGCG AGCGGTTGCT
 AAGGTGCGTC CCGCGCTCGA CGCCGTACCG GACTTAGCGC TCGCCAACGA
 10101 GCGCGAGGAG GACTTTGAGC CCGACGCGCG AACCGGGATT AGTCCCGCGC
 CGCGCTCCTC CTGAAACTCG GGCTGCGCGC TTGGCCCTAA TCAGGGCGCG
 10151 GCGCACACGT GCGGGCCGCC GACCTGGTAA CCGCATACGA GCAGACGGTG
 CGCGTGTGCA CCGCCGGCGG CTGGACCATT GCGGTATGCT CGTCTGCCAC
 10201 AACCAGGAGA TTAACCTTCA AAAAAGCTTT AACCAACCAG TGGGTACGCT
 TTGGTCTCTT AATTGAAAGT TTTTTCGAAA TTGTTGGTGC ACGCATGCGA
 10251 TGTGGCGCGC GAGGAGGTGG CTATAGGACT GATGCATCTG TGGGACTTTG
 ACACCGCGCG CTCTCCACC GATATCCTGA CTACGTAGAC ACCCTGAAAC
 10301 TAAGCGCGCT GGAGCAAAAC CCAAATAGCA AGCCGCTCAT GGCGCAGCTG
 ATTCGCGCGA CCTCGTTTTG GGTTTATCGT TCGGCGAGTA CCGCGTCGAC

Figure 27K

10401 GCTAAACATA GTAGAGCCCG AGGGCCGCTG GCTGCTCGAT TTGATAAACA
CGATTTGTAT CATCTCGGGC TCCC GGCGAC CGACGAGCTA AACTATTTGT

10451 TCCTGCAGAG CATAGTGGTG CAGGAGCGCA GCTTGAGCCT GGCTGACAAG
AGGACGTCTC GTATCACCAC GTCCTCGCGT CGAACTCGGA CCGACTGTTC

10501 GTGGCCGCCA TCAACTATTC CATGCTTAGC CTGGGCAAGT TTTACGCCCC
CACCGGCGGT AGTTGATAAG GTACGAATCG GACCCGTTCA AAATGCGGGC

10551 CAAGATATAC CATACCCCTT ACGTTCCCAT AGACAAGGAG GTAAAGATCG
GTTCTATATG GTATGGGGAA TGCAAGGGTA TCTGTTCTCT CATTCTAGC

10601 AGGGGTTCTA CATGCGCATG GCGCTGAAGG TGCTTACCTT GAGCGACGAC
TCCCAAGAT GTACGCGTAC CGCGACTTCC ACGAATGGAA CTCGCTGCTG

10651 CTGGGCGTTT ATCGCAACGA GCGCATCCAC AAGGCCGTGA GCGTGAGCCG
GACCCGCAA TAGCGTTGCT CGCGTAGGTG TTCCGGCACT CGCACTCGGC

10701 GCGGCGCGAG CTCAGCGACC GCGAGCTGAT GCACAGCCTG CAAAGGGCCC
CGCCGCGCTC GAGTCGCTGG CGCTCGACTA CGTGTCGGAC GTTTCCTGGG

10751 TGGCTGGCAC GGGCAGCGGC GATAGAGAGG CCGAGTCCTA CTTTGACGCG
ACCGACCGTG CCCGTCGCCG CTATCTCTCC GGCTCAGGAT GAAACTGCGC

10801 GCGCTGACC TGCGCTGGGC CCCAAGCCGA CGCGCCCTGG AGGCAGCTGG
CCGCGACTGG ACGCGACCCG GGGTTCCGGT GCGCGGGACC TCCGTCGACC

10851 GGCCGGACCT GGGCTGGCGG TGGCACCCGC GCGCGCTGGC AACGTCGGCG
CCGGCCTGGA CCCGACCGCC ACCGTGGGCG CGCGCGACCG TTGCAGCCGC

10901 GCGTGAGGA ATATGACGAG GACGATGAGT ACGAGCCAGA GGACGGCGAG
CGCACCTCCT TATACTGCTC CTGCTACTCA TGCTCGGTCT CCTGCCGCTC

10951 TACTAAGCGG TGATGTTTCT GATCAGATGA TGCAAGACGC AACGGACCCG
ATGATTCGCC ACTACAAAGA CTAGTCTACT ACGTTCTGCG TTGCCTGGGC

11001 GCGGTGCGGG CGGCGCTGCA GAGCCAGCCG TCCGGCCTTA ACTCCACGGA
CGCCACGCCC GCCGCGACGT CTCGGTCGGC AGGCCGGAAT TGAGGTGCCT

11051 CGACTGGCGC CAGGTCATGG ACCGCATCAT GTCGCTGACT GCGCGCAATC
GCTGACCGCG GTCCAGTACC TGGCGTAGTA CAGCGACTGA CGCGCGTTAG

11101 CTGACGCGTT CCGGCAGCAG CCGCAGGCCA ACCGGCTCTC CGCAATTCTG
GACTGCGCAA GGCCGTCGTC GGCGTCCGGT TGGCCGAGAG GCGTTAAGAC

11151 GAAGCGGTGG TCCCGGCGCG CGCAAACCCC ACGCACGAGA AGGTGCTGGC
CTTCGCCACC AGGGCCGCGC GCGTTTGGGG TGCGTGCTCT TCCACGACCG

11201 GATCGTAAAC GCGCTGGCCG AAAACAGGGC CATCCGGCCC GACGAGGCCG
CTAGCATTTG CGCGACCGGC TTTTGTCCCG GTAGGCCGGG CTGCTCCGGC

11251 GCCTGGTCTA CGACGCGCTG CTTAGCGCG TGGCTCGTTA CAACAGCGGC
CGGACCAGAT GCTGCGCGAC GAAGTCGCGC ACCGAGCAAT GTTGTCGCCC

Figure 27L

11351 GGCGCAGCGT GAGCGCGCGC AGCAGCAGGG CAACCTGGGC TCCATGGTTG
 CCGCGTCGCA CTCGCGCGCG TCGTCGTCCC GTTGGACCCG AGGTACCAAC
 11401 CACTAAACGC CTTCTGAGT ACACAGCCCG CCAACGTGCC GCGGGGACAG
 GTGATTTGCG GAAGGACTCA TGTGTCGGGC GGTGTCACGG CGCCCTGTG
 11451 GAGGACTACA CCAACTTTGT GAGCGCACTG CGGCTAATGG TGA CTGAGAC
 CTCCTGATGT GGTGAAACA CTCGCGTGAC GCCGATTACC ACTGACTCTG
 11501 ACCGCAAAGT GAGGTGTACC AGTCTGGGCC AGACTATTTT TTCCAGACCA
 TGGCGTTTCA CTCCACATGG TCAGACCCGG TCTGATAAAA AAGGTCTGGT
 11551 GTAGACAAGG CCTGCAGACC GTAAACCTGA GCCAGGCTTT CAAAACTTG
 CATCTGTTCC GGACGTCTGG CATTGACT CGGTCCGAAA GTTTTGAAC
 11601 CAGGGGCTGT GGGGGGTGCG GGCTCCACA GCGACCGCG CGACCGTGTC
 GTCCCCGACA CCCCCACGC CCGAGGGTGT CCGCTGGCGC GCTGGCACAG
 11651 TAGCTTGCTG ACGCCCACT CGCGCCTGTT GCTGCTGCTA ATAGCGCCCT
 ATCGAACGAC TCGGGTTGA GCGCGGACAA CGACGACGAT TATCGCGGGA
 11701 TCACGGACAG TGGCAGCGTG TCCCGGGACA CATACTAGG TCACTTGCTG
 AGTGCCTGTC ACCGTCGCAC AGGGCCCTGT GTATGGATCC AGTGAACGAC
 11751 ACACTGTACC GCGAGGCCAT AGGTCAGGCG CATGTGGACG AGCATACTTT
 TGTGACATGG CGCTCCGGTA TCCAGTCCGC GTACACCTGC TCGTATGAAA
 11801 CCAGGAGATT ACAAGTGTCA GCCGCGCGCT GGGGCAGGAG GACACGGGCA
 GGTCTCTAA TGTTCACAGT CGGCGCGCA CCCCCTCTC CTGTGCCCGT
 11851 GCCTGGAGGC AACCCTAAAC TACCTGCTGA CCAACCGGCG GCAGAAGATC
 CGGACCTCCG TTGGGATTTG ATGGACGACT GGTGGCCGC CGTCTTCTAG
 11901 CCCTCGTTGC ACAGTTTAAA CAGCGAGGAG GAGCGCATTT TGCGCTACGT
 GGGAGCAACG TGTCAAATTT GTCGCTCCTC CTCGCGTAAA ACGCGATGCA
 11951 GCAGCAGAGC GTGAGCCTTA ACCTGATGCG CGACGGGGTA ACGCCACGCG
 CGTCGTCTCG CACTCGGAAT TGGACTACGC GCTGCCCCAT TGCGGGTCGC
 12001 TGGCGCTGGA CATGACCGCG CGCAACATGG AACC GGCGAT GTATGCCTCA
 ACCGCGACCT GTACTGGCGC GCGTTGTACC TTGGCCCGTA CATACGGAGT
 12051 AACC GGCGCT TTATCAACCG CCTAATGGAC TACTTGATC GCGCGGCCG
 TTGGCCGGCA AATAGTTGGC GGATTACCTG ATGAACGTAG CGCGCCGGCG
 12101 CGTGAACCCC GAGTATTTCA CCAATGCCAT CTTGAACCCG CACTGGCTAC
 GCACTTGGGG CTCATAAAGT GGTACGGTA GAACTTGGGC GTGACCGATG
 12151 CGCCCCCTGG TTTCTACACC GGGGGATTG AGGTGCCCCG GGGTAACGAT
 GCGGGGGACC AAAGATGTGG CCCCCTAAGC TCCACGGGCT CCCATTGCTA
 12201 GGATTCTCTT GGGACGACAT AGACGACAGC GTGTTTTCCC CGCAACCGCA
 CCTAAGGAGA CCCTGCTGTA TCTGCTGTCG CACAAAAGGG GCGTTGGCGT

Figure 27 M

12301 AGGAAAGCTT CCGCAGGCCA AGCAGCTTGT CCGATCTAGG CGCTGCGGCC
 TCCTTTTCGAA GGC GTCCGGT TCGTCGAACA GGCTAGATCC GCGACGCCGG

12351 CCGCGGTCTAG ATGCTAGTAG CCCATTTCCA AGCTTGATAG GGTCTCTTAC
 GGCGCCAGTC TACGATCATC GGGTAAAGGT TCGAACTATC CCAGAGAATG

12401 CAGCACTCGC ACCACCCGCC CGCGCCTGCT GGGCGAGGAG GAGTACCTAA
 GTCGTGAGCG TGGTGGGCGG GCGCGGACGA CCCGCTCCTC CTCATGGATT

12451 ACAACTCGCT GCTGCAGCCG CAGCGCGAAA AAAACCTGCC TCCGGCATTT
 TGTTGAGCGA CGACGTCGGC GTCGCGCTTT TTTTGGACGG AGGCCGTAAA

12501 CCCAACAAACG GGATAGAGAG CCTAGTGGAC AAGATGAGTA GATGGAAGAC
 GGGTTGTTCG CCTATCTCTC GGATCACCTG TTCTACTCAT CTACCTTCTG

12551 GTACGCGCAG GAGCACAGGG ACGTGCCAGG CCCGCGCCCG CCCACCCGTC
 CATGCGCGTC CTCGTGTCCC TGCACGGTCC GGGCGCGGGC GGGTGGGCAG

12601 GTCAAAGGCA CGACCGTCAG CGGGGTCTGG TGTGGGAGGA CGATGACTCG
 CAGTTTCCGT GCTGGCAGTC GCCCCAGACC ACACCTCCT GCTACTGAGC

12651 GCAGACGACA GCAGCGTCCT GGATTTGGGA GGGAGTGGCA ACCCGTTTGC
 CGTCTGCTGT CGTCGCAGGA CCTAAACCT CCCTCACCCT TGGGCAAACG

12701 GCACCTTCGC CCCAGGCTGG GGAGAAATGTT TTAACAAAAA AAAAAGCATG
 CGTGGAAGCG GGGTCCGACC CCTCTTACAA AATTTTTTTT TTTTTCGTAC

12751 ATGCAAAATA AAAAATCAC CAAGGCCATG GCACCGAGCG TTGGTTTTCT
 TACGTTTTAT TTTTGTAGTG GTTCCGGTAC CGTGGCTCGC AACCAAAAGA

12801 TGTATTCCCC TTAGTATGCG GCGCGCGGCG ATGTATGAGG AAGGTCCTCC
 ACATAAGGGG AATCATACGC CGCGCGCCGC TACATACTCC TTCCAGGAGG

12851 TCCCTCCTAC GAGAGTGTGG TGAGCGCGGC GCCAGTGGCG GCGGCGCTGG
 AGGGAGGATG CTCTCACACC ACTCGCGCCG CGGTACCCGC CGCCGCGACC

12901 GTTCTCCCTT CGATGCTCCC CTGGACCCGC CGTTTGTGCC TCCGCGGTAC
 CAAGAGGGAA GCTACGAGGG GACCTGGGCG GCAAACACGG AGGCGCCATG

12951 CTGCGGCCTA CCGGGGGGAG AAACAGCATC CGTTACTCTG AGTTGGCACC
 GACGCCGGAT GGCCCCCTC TTTGTCTAG GCAATGAGAC TCAACCGTGG

13001 CCTATTGAC ACCACCCGTG TGTACCTGGT GGACAACAAG TCAACGGATG
 GGATAAGCTG TGGTGGGCAC ACATGGACCA CCTGTTGTTT AGTTGCCTAC

13051 TGGCATCCCT GAACTACCAG AACGACCACA GCAACTTTCT GACCACGGTC
 ACCGTAGGGA CTGATGGTC TTGCTGGTGT CGTTGAAAGA CTGGTGCCAG

13101 ATTCAAACA ATGACTACAG CCCGGGGGAG GCAAGCACAC AGACCATCAA
 TAAGTTTGT TACTGATGTC GGGCCCCCTC CGTTCTGTGT TCTGGTAGTT

13151 TCTTGACGAC CGGTCGCACT GGGGCGGCGA CCTGAAAACC ATCCTGCATA
 AGAACTGCTG GCCAGCGTGA CCCC GCCGCT GGACTTTTGG TAGGACGTAT

Figure 27N

13251 CGGGTGATGG TGTGCGCCTT GCCTACTAAG GACAATCAGG TGGAGCTGAA
GCCCCTACC ACAGCGCGAA CGGATGATTC CTGTTAGTCC ACCTCGACTT

13301 ATACGAGTGG GTGGAGTTCA CGCTGCCCCG GGGCAACTAC TCCGAGACCA
TATGCTCACC CACCTCAAGT GCGACGGGCT CCCGTTGATG AGGCTCTGGT

13351 TGACCATAGA CCTTATGAAC AACGCGATCG TGGAGCACTA CTTGAAAGTG
ACTGGTATCT GGAATACTTG TTGCGCTAGC ACCTCGTGAT GAACTTTCAC

13401 GGCAGACAGA ACGGGGTTCT GGAAAGCGAC ATCGGGGTAA AGTTTGACAC
CCGTCTGTCT TGCCCCAAGA CCTTTCGCTG TAGCCCCATT TCAAACGTGTG

13451 CCGCAACTTC AGACTGGGGT TTGACCCCGT CACTGGTCTT GTCATGCCTG
GGCGTTGAAG TCTGACCCCA AACTGGGGCA GTGACCAGAA CAGTACGGAC

13501 GGGTATATAC AAACGAAGCC TTCCATCCAG ACATCATTTT GCTGCCAGGA
CCCATATATG TTTGCTTCGG AAGGTAGGTC TGTAATAAAA CGACGGTCCCT

13551 TGGGGGGTGG ACTTCACCCA CAGCCGCCTG AGCAACTTGT TGGGCATCCG
ACGCCCCACC TGAAGTGGGT GTCGGCGGAC TCGTTGAACA ACCCGTAGGC

13601 CAAGCGGCAA CCCTTCCAGG AGGGCTTTAG GATCACCTAC GATGATCTGG
GTTGCGCGTT GGGAAGGTCC TCCCGAAATC CTAGTGGATG CTACTAGACC

13651 AGGGTGGTAA CATTCCCGCA CTGTTGGATG TGGACGCCTA CCAGGCGAGC
TCCCACCATT GTAAGGGCGT GACAACCTAC ACCTGCGGAT GGTCCGCTCG

13701 TTGAAAGATG ACACCGAACA GGGCGGGGGT GGCGCAGGCG GCAGCAACAG
AACTTTCTAC TGTGGCTTGT CCCGCCCCCA CCGCGTCCGC CGTCGTTGTC

13751 CAGTGGCAGC GGCGCGGAAG AGAACTCCAA CGCGGCAGCC GCGGCAATGC
GTCAECGTCTG CCGCGCCTTC TCTTGAGGTT GCGCCGTCTG CGCCGTTACG

13801 AGCCGGTGGA GGACATGAAC GATCATGCCA TTCGCGGCGA CACCTTTGCC
TCGGCCACCT CCTGTACTTG CTAGTACGGT AAGCGCCGCT GTGGAAACGG

13851 ACACGGGCTG AGGAGAAGCG CGCTGAGGCC GAAGCAGCGG CCGAAGCTGC
TGTGCCCCGAC TCCTCTTCGC GCGACTCCGG CTTCGTCTGC GGCTTCGACG

13901 CGCCCCCGCT GCGCAACCCG AGGTCGAGAA GCCTCAGAAG AAACCGGTGA
GCGGGGGCGA CGCGTTGGGC TCCAGCTCTT CGGAGTCTTC TTTGGCCACT

13951 TCAAACCCCT GACAGAGGAC AGCAAGAAAC GCAGTTACAA CCTAATAAGC
AGTTTGGGGA CTGTCTCCTG TCGTTCCTTG CGTCAATGTT GGATTATTCTG

14001 AATGACAGCA CCTTCACCCA GTACCGCAGC TGGTACCTTG CATACTACTA
TACTGTCTGT GGAAGTGGGT CATGGCGTCTG ACCATGGAAC GTATGTTGAT

14051 CGGCGACCCT CAGACCGGAA TCCGCTCATG GACCCCTGCTT TGCCTCCTG
GCCGCTGGGA GTCTGGCCTT AGGCGAGTAC CTGGGACGAA ACGTGAGGAC

14101 ACGTAACCTG CGGCTCGGAG CAGGTCTACT GGTCGTTGCC AGACATGATG
TGCATTGGAC GCCGAGCCTC GTCCAGATGA CCAGCAACGG TCTGTACTAC

Figure 270

14201 GGTGGGCGCC GAGCTGTTGC CCGTGCACTC CAAGAGCTTC TACAACGACC
CCACCCGCGG CTCGACAACG GGCACGTGAG GTTCTCGAAG ATGTTGCTGG

14251 AGGCCGTCTA CTCCCAACTC ATCCGCCAGT TTACCTCTCT GACCCACGTG
TCCGGCAGAT GAGGGTTGAG TAGGCGGTCA AATGGAGAGA CTGGGTGCAC

14301 TTCAATCGCT TTCCCGAGAA CCAGATTTTG GCGCGCCCGC CAGCCCCCAC
AAGTTAGCGA AAGGGCTCTT GGTCTAAAAC CGCGCGGGCG GTCGGGGGTG

14351 CATCACCACC GTCAGTGAAG ACGTTCCTGC TCTCACAGAT CACGGGACGC
GTAGTGGTGG CAGTCACTTT TGCAAGGACG AGAGTGTCTA GTGCCCTGCG

14401 TACCGCTGCG CAACAGCATC GGAGGAGTCC AGCGAGTGAC CATTACTGAC
ATGGCGACGC GTTGTCTGAG CCTCCTCAGG TCGCTCACTG GTAATGACTG

14451 GCCAGACGCC GCACCTGCCC CTACGTTTAC AAGGCCCTGG GCATAGTCTC
CGGTCTGCGG CGTGGACGGG GATGCAAATG TTCCGGGACC CGTATCAGAG

14501 GCCGCGCGTC CTATCGAGCC GCACTTTTTC AGCAAGCATG TCCATCCTTA
CGCGCGCAG GATAGCTCGG CGTGAAAAAC TCGTTCGTAC AGGTAGGAAT

14551 TATCGCCCAG CAATAACACA GGCTGGGGCC TGCCTTCCC AAGCAAGATG
ATAGCGGGTC GTTATTGTGT CCGACCCCGG ACGCGAAGGG TTCGTTCTAC

14601 TTTGGCGGGG CCAAGAAGCG CTCCGACCAA CACCCAGTGC GCGTGCGCGG
AAACCGCCCC GGTCTTTCGC GAGGCTGGTT GTGGGTCACG CGCACGCGCC

14651 GCACTACCGC GCGCCCTGGG GCGCGCACAA ACGCGGCCGC ACTGGGCGCA
CGTGATGGCG CGCGGGACCC CGCGCGTGTT TGCGCCGGCG TGACCCGCGT

14701 CCACCGTCGA TGACGCCATC GACGCGGTGG TGGAGGAGGC GCGCAACTAC
GGTGGCAGCT ACTGCGGTAG CTGCGCCACC ACCTCCTCCG CGCGTTGATG

14751 ACGCCACGCG CGCCACCAGT GTCCACAGTG GACGCGGCCA TTCAGACCGT
TGCGGGTGCG GCGGTGGTCA CAGGTGTCAC CTGCGCCGGT AAGTCTGGCA

14801 GGTGCGCGGA GCCCGGCGCT ATGCTAAAAT GAAGAGACGG CGGAGGCGCG
CCACGCGCCT CGGGCCGCGA TACGATTTTA CTTCTCTGCC GCCTCCGCGC

14851 TAGCACGTCG CCACCGCCGC CGACCCGGCA CTGCCGCCA ACGCGCGGCG
ATCGTGACG GGTGGCGGCG GCTGGGCCGT GACGGCGGGT TGCGCGCCGC

14901 GCGGCCCTGC TTAACCGCGC ACGTCGCACC GGCCGACGGG CGGCCATGCG
CGCCGGGACG AATTGGCGCG TGCAGCGTGG CCGGCTGCCC GCCGGTACGC

14951 GGCCGCTCGA AGGCTGGCCG CGGGTATTGT CACTGTGCCC CCCAGGTCCA
CCGGCGAGCT TCCGACCGGC GCCCATAACA GTGACACGGG GGGTCCAGGT

15001 GCGGACGAGC GGCCGCCGCA GCAGCCGCGG CCATTAGTGC TATGACTCAG
CCGCTGCTCG CCGGCGGCGT CGTCGGCGCC GGTAATCACG ATACTGAGTC

15051 GGTGCGAGGG GCAACGTGTA TTGGGTGCGC GACTCGGTTA GCGGCCTGCG
CCAGCGTCCC CGTTGCACAT AACCCACGCG CTGAGCCAAT CGCCGGACGC

Figure 27P

15151 ACTTAGACTC GTACTGTTGT ATGTATCCAG CGGCGGCGGC GCGCAACGAA
TGAATCTGAG CATGACAACA TACATAGGTC GCCGCCGCCG CGCGTTGCTT

15201 GCTATGTCCA AGCGCAAAAT CAAAGAAGAG ATGCTCCAGG TCATCGCGCC
CGATACAGGT TCGCGTTTTA GTTCTTCTC TACGAGGTCC AGTAGCGCGG

15251 GGAGATCTAT GGCCCCCGA AGAAGGAAGA GCAGGATTAC AAGCCCCGAA
CCTCTAGATA CCGGGGGGCT TCTTCTTCT CGTCCTAATG TTCGGGGGCTT

15301 AGCTAAAGCG GGTCAAAAAG AAAAAGAAAG ATGATGATGA TGAAC TTGAC
TCGATTTTCG CCAGTTTTTC TTTTCTTTC TACTACTACT ACTTGAAC TG

15351 GACGAGGTGG AACTGCTGCA CGCTACCGCG CCCAGGCGAC GGGTACAGTG
CTGCTCCACC TTGACGACGT GCGATGGCGC GGGTCCGCTG CCCATGTCAC

15401 GAAAGGTCGA CGCGTAAAC GTGTTTTGCG ACCCGGCACC ACCGTAGTCT
CTTTCAGCT GCGCATTTTG CACAAAACGC TGGGCCGTGG TGGCATCAGA

15451 TTACGCCCGG TGAGCGCTCC ACCCGCACCT ACAAGCGCGT GTATGATGAG
AATGCGGGCC ACTCGCGAGG TGGGCGTGGA TGTTGCGCA CATACTACTC

15501 GTGTACGGCG ACAGGACCT GCTTGAGCAG GCCAACGAGC GCCTCGGGGA
CACATGCCGC TGCTCCTGGA CGAACTCGTC CGGTTGCTCG CGGAGCCCCT

15551 GTTTGCCTAC GGAAAGCGGC ATAAGGACAT GCTGGCGTTG CCGCTGGACG
CAAACGGATG CCTTTCGCCG TATTCCTGTA CGACCGCAAC GGCGACCTGC

15601 AGGGCAACCC AACACCTAGC CTAAAGCCCC TAACACTGCA GCAGGTGCTG
TCCCGTTGGG TTGTGGATCG GATTTCGGGC ATTGTGACGT CGTCCACGAC

15651 CCCGCGCTTG CACCGTCCGA AGAAAAGCGC GGCCTAAAGC GCGAGTCTGG
GGGCGCGAAC GTGGCAGGCT TCTTTTCGCG CCGGATTTCG CGCTCAGACC

15701 TGACTTGGA CCCACCGTGC AGCTGATGGT ACCCAAGCGC CAGCGACTGG
ACTGAACCGT GGGTGGCAGC TCGACTACCA TGGGTTCGCG GTCGCTGACC

15751 AAGATGTCTT GGAAAAATG ACCGTGGAAC CTGGGCTGGA GCCCGAGGTC
TTCTACAGAA CCTTTTTTAC TGGCACCTTG GACCCGACCT CGGGCTCCAG

15801 CGCGTGCGGC CAATCAAGCA GGTGGCGCCG GGAAGGGCG TGCAGACCGT
GCGCACGCCG GTTAGTTCTG CCACCGCGGC CCTGACCGC ACCTCTGGCA

15851 GGACGTTTCTG ATACCCACTA CCAGTAGCAC CAGTATTGCC ACCGCCACAG
CCTGCAAGTC TATGGGTGAT GGTATCTGTC GTCATAACGG TGGCGGTGTC

15901 AGGGCATGGA GACACAAACG TCCCCGGTTG CTTAGCGGT GCGGATGCC
TCCCGTACCT CTGTGTTTGC AGGGGCCAAC GGAGTCGCCA CCGCTACGG

15951 GCGGTGCAGG CGGTCGCTGC GGCCGCGTCC AAGACCTCTA CGGAGGTGCA
GCCACGTCC GCCAGCGACG CCGGCGCAGG TTCTGGAGAT GCCTCCACGT

16001 AACGGACCCG TGGATGTTTC GCGTTTCAGC CCCCCGGCGC CCGCGCCGTT
TTGCCTGGGC ACCTACAAAG CGCAAAGTCG GGGGGCCGCG GGCGCGGCAA

Figure 27Q

16051 CGAGGAAAGTA CGGCGCCGCC AGCGCGCTAC TGCCCCGAATA TGCCCTACAT
GCTCCTTCAT GCCGCGGCGG TCGCGCGATG ACGGGCTTAT ACGGGATGTA

16101 CCTTCCATTG CGCCTACCCC CGGCTATCGT GGCTACACCT ACCGCCCCAG
GGAAGGTAAC GCGGATGGGG GCCGATAGCA CCGATGTGGA TGGCGGGGTC

16151 AAGACGAGCA ACTACCCGAC GCCGAACCAC CACTGGAACC CGCCGCCGCC
TTCTGCTCGT TGATGGGCTG CGGCTTGGTG GTGACCTTGG GCGGCGGCGG

16201 GTCGCCGTCG CCAGCCCGTG CTGGCCCCGA TTTCCGTGCG CAGGGTGGCT
CAGCGGCAGC GGTCGGGCAC GACCGGGGCT AAAGGCACGC GTCCACCGA

16251 CGCGAAGGAG GCAGGACCTT GGTGCTGCCA ACAGCGCGCT ACCACCCCAG
GCGCTTCCTC CGTCCTGGGA CCACGACGGT TGTCGCGCGA TGGTGGGGTC

16301 CATCGTTTAA AAGCCGGTCT TTGTGGTTCT TGCAGATATG GCCCTCACCT
GTAGCAAATT TTCGGCCAGA AACACCAAGA ACGTCTATAC CGGGAGTGGGA

16351 GCCGCCTCCG TTTCCCGGTG CCGGGATTCC GAGGAAGAAT GCACCGTAGG
CGGCGGAGGC AAAGGGCCAC GGCCCTAAGG CTCCTTCTTA CGTGGCATCC

16401 AGGGGCATGG CCGGCCACGG CCTGACGGGC GGCATGCGTC GTGCGCACCA
TCCCCGTACC GGCCGGTGCC GGACTGCCCC CCGTACGCAG CACGCGTGGT

16451 CCGGCGGCGG CGCGCGTCGC ACCGTGCGAT GCGCGGCGGT ATCCTGCCCC
GGCCGCCGCC GCGCGCAGCG TGGCAGCGTA CCGCGCGCCA TAGGACGGGG

16501 TCCTTATTCC ACTGATCGCC GCGGCGATTG GCGCCGTGCC CGGAATTGCA
AGGAATAAGG TGA TAGCGG CGCCGCTAAC CCGGCGACGG GCCTTAACGT

16551 TCCGTGGCCT TGCAGGCGCA GAGACACTGA TTAAAAACAA GTTGCATGTG
AGGCACCGGA ACGTCCGCGT CTCTGTGACT AATTTTGTGTT CAACGTACAC

16601 GAAAAATCAA AATAAAAAGT CTGGACTCTC ACGCTCGCTT GGTCTGTAA
CTTTTGTAGTT TTATTTTCA GACCTGAGAG TGCGAGCGAA CCAGGACATT

16651 CTATTTTGTA GAATGGAAGA CATCAACTTT GCGTCTCTGG CCCC GCGACA
GATAAAACAT CTTACCTTCT GTAGTTGAAA CGCAGAGACC GGGGCGCTGT

16701 CGGCTCGCGC CCGTTCATGG GAAACTGGEA AGATATCGGC ACCAGCAATA
GCCGAGCGCG GGCAAGTACC CTTTGACCGT TCTATAGCCG TGGTCGTTAT

16751 TGAGCGGTGG CGCCTTCAGC TGGGGCTCGC TGTGGAGCGG CATTAAAAAT
ACTCGCCACC GCGGAAGTCG ACCCCGAGCG ACACCTCGCC GTAATTTTAA

16801 TTCGGTTCCA CCGTTAAGAA CTATGGCAGC AAGGCCTGGA ACAGCAGCAC
AAGCCAAGGT GGCAATTCTT GATACCGTCG TTCCGGACCT TGTCGTCGTG

16851 AGGCCAGATG CTGAGGGATA AGTTGAAAGA GCAAAATTTT CAACAAAAGG
TCCGGTCTAC GACTCCCTAT TCAACTTTCT CGTTTTAAAG GTTGTTTTCC

16901 TGGTAGATGG CCTGGCCTCT GGCATTAGCG GGGTGGTGGG CCTGGCCAAC
ACCATCTACC GGACCGGAGA CCGTAATCGC CCCACCACCT GGACCGGTTG

16951 CAGGCAGTGC AAAATAAGAT TAACAGTAAG CTTGATCCCC GCCCTCCCGT
GTCCGTCACG TTTTATTCTA ATTGTCATTC GAACTAGGGG CGGGAGGGCA

Figure 27R

17051 AAAAGCGTCC GCGCCCCGAC AGGGAAGAAA CTCTGGTGAC GCAAATAGAC
TTTTTCGCAGG CGCGGGGCTG TCCCTTCTTT GAGACCACTG CGTTTATCTG

17101 GAGCCTCCCT CGTACGAGGA GGCCTAAAG CAAGGCCTGC CCACCACCCG
CTCGGAGGGA GCATGCTCCT CCGTGATTTC GTTCCGGACG GGTGGTGGGC

17151 TCCCATCGCG CCCATGGCTA CCGGAGTGCT GGGCCAGCAC ACACCCGTAA
AGGGTAGCGC GGGTACCGAT GGCCTCACGA CCCGGTCGTG TGTGGGCATT

17201 CGCTGGACCT GCCTCCCCC GCCGACACCC AGCAGAAACC TGTGCTGCCA
GCGACCTGGA CGGAGGGGGG CGGCTGTGGG TCGTCTTTGG ACACGACGGT

17251 GGCCCCGACCG CCGTTGTTGT AACCCTGCTCT AGCCGCGCGT CCCTGCGCCG
CCGGGCTGGC GGCAACAACA TTGGGCAGGA TCGGCGCGCA GGGACGCGGC

17301 CGCCGCCAGC GGTCCGCGAT CGTTGCGGCC CGTAGCCAGT GGCAACTGGC
GCGGCGGTGCG CCAGGCGCTA GCAACGCCGG GCATCGGTCA CCGTTGACCG

17351 AAAGCACACT GAACAGCATC GTGGGTCTGG GGGTGCAATC CCTGAAGCGC
TTTCGTGTGA CTTGTCGTAG CACCCAGACC CCCACGTTAG GGACTTCGCG

17401 CGACGATGCT TCTGATAGCT AACGTGTCGT ATGTGTGTCA TGTATGCGTC
GCTGCTACGA AGACTATCGA TTGCACAGCA TACACACAGT ACATACGCAG

17451 CATGTCGCGG CCAGAGGAGC TGCTGAGCCG CCGCGCGCCC GCTTTCCAAG
GTACAGCGGC GGTCTCCTCG ACGACTCGGC GGC GCGCGGG CGAAAGGTTC

17501 ATGGCTACCC CTTGATGAT GCCGCAGTGG TCTTACATGC ACATCTCGGG
TACCGATGGG GAAGCTACTA CGGCGTCACC AGAATGTACG TGTAGAGCCC

17551 CCAGGACGCC TCGGAGTACC TGAGCCCCGG GCTGGTGCAG TTTGCCCCGG
GGTCTGCGG AGCCTCATGG ACTCGGGGCC CGACCACGTC AAACGGGCGC

17601 CCACCGAGAC GTACTTCAGC CTGAATAACA AGTTTAGAAA CCCCACGGTG
GGTGGCTCTG CATGAAGTCG GACTTATTGT TCAAATCTTT GGGGTGCCAC

17651 GCGCCTACGC ACGACGTGAC CACAGACCGG TCCCAGCGTT TGACGCTGCG
CGCGGATGCG TGCTGCACTG GTGTCTGGCC AGGGTCGCAA ACTGCGACGC

17701 GTTCATCCCT GTGGACCGTG AGGATACTGC GTACTCGTAC AAGGCGCGGT
CAAGTAGGGA CACCTGGCAC TCCTATGACG CATGAGCATG TTCCGCGCCA

17751 TCACCCTAGC TGTGGGTGAT AACCGTGTGC TGGACATGGC TTCCACGTAC
AGTGGGATCG ACACCCACTA TTGGCACACG ACCTGTACCG AAGGTGCATG

17801 TTTGACATCC GCGGCGTGCT GGACAGGGGC CCTACTTTTA AGCCCTACTC
AAACTGTAGG CGCCGCACGA CCTGTCCCCG GGATGAAAAT TCGGGATGAG

17851 TGGCACTGCC TACAACGCCC TGGCTCCCAA GGGTGCCCCA AATCCTTGCG
ACCGTGACGG ATGTTGCGGG ACCGAGGGTT CCCACGGGGT TTAGGAACGC

17901 AATGGGATGA AGCTGCTACT GCTCTTGAAA TAAACCTAGA AGAAGAGGAC
TTACCCTACT TCGACGATGA CGAGAACTTT ATTTGGATCT TCTTCTCCTG

Figure 275

17951 GATGACAACG AAGACGAAGT AGACGAGCAA GCTGAGCAGC AAAAACTCA
CTACTGTTGC TTCTGCTTCA TCTGCTCGTT CGACTCGTCG TTTTGTGAGT

18001 CGTATTTGGG CAGGCGCCTT ATTCTGGTAT AAATATTACA AAGGAGGGTA
GCATAAACCC GTCCGCGGAA TAAGACCATA TTTATAATGT TTCCTCCCAT

18051 TTCAAATAGG TGTCGAAGGT CAAACACCTA AATATGCCGA TAAAACATTT
AAGTTTATCC ACAGCTTCCA GTTTGTGGAT TTATACGGCT ATTTTGTAAA

18101 CAACCTGAAC CTCAAATAGG AGAATCTCAG TGGTACGAAA CAGAAATTAA
GTTGGACTTG GAGTTTATCC TCTTAGAGTC ACCATGCTTT GTCTTTAATT

18151 TCATGCAGCT GGGAGAGTCC TAAAAAAGAC TACCCCAATG AAACCATGTT
AGTACGTCGA CCCTCTCAGG ATTTTTTCTG ATGGGGTTAC TTTGGTACAA

18201 ACGGTTTATA TGCAAAACCC ACAAAATGAAA ATGGAGGGCA AGGCATTCTT
TGCCAAGTAT ACGTTTTGGG TGTTTACTTT TACCTCCCGT TCCGTAAGAA

18251 GTAAAGCAAC AAAATGGAAA GCTAGAAAGT CAAGTGGAAA TGCAATTTTT
CATTTCTGTTG TTTTACCTTT CGATCTTTCA GTTCACCTTT ACGTTAAAAA

18301 CTCAACTACT GAGGCAGCCG CAGGCAATGG TGATAACTTG ACTCCTAAAG
GAGTTGATGA CTCCGTCGGC GTCCGTTACC ACTATTGAAC TGAGGATTTT

18351 TGGTATTGTA CAGTGAAGAT GTAGATATAG AAACCCCAAG CACTCATATT
ACCATAACAT GTCACCTTCTA CATCTATATC TTTGGGGTCT GTGAGTATAA

18401 TCTTACATGC CCACTATTAA GGAAGGTAAC TCACGAGAAC TAATGGGCCA
AGAATGTACG GGTGATAATT CCTTCCATTG AGTGCTCTTG ATTACCCGGT

18451 ACAATCTATG CCCAACAGGC CTAATTACAT TGCTTTTAGG GACAATTTTA
TGTTAGATAC GGGTTGTCCG GATTAATGTA ACGAAAATCC CTGTTAAAAT

18501 TTGGTCTAAT GTATTACAAC AGCACGGGTA ATATGGGTGT TCTGGCGGGC
AACCAGATTA CATAATGTTG TCGTGCCCAT TATACCCACA AGACCGCCCG

18551 CAAGCATCGC AGTTGAATGC TGTGTAGAT TTGCAAGACA GAAACACAGA
GTTTCGTAGC TCAACTTACG ACAACATCTA AACGTTCTGT CTTTGTGTCT

18601 GCTTTCATAC CAGCTTTTGC TTGATTCCAT TGGTGATAGA ACCAGGTACT
CGAAAGTATG GTCGAAAACG AACTAAGGTA ACCACTATCT TGGTCCATGA

18651 TTTCTATGTG GAATCAGGCT GTTGACAGCT ATGATCCAGA TGTTAGAATT
AAAGATACAC CTTAGTCCGA CAACTGTCTA TACTAGGTCT ACAATCTTAA

18701 ATTGAAAATC ATGGAAGTGA AGATGAACTT CCAAATTACT GCTTTCCACT
TAACTTTTAG TACCTTGACT TCTACTTGAA GGTTTAATGA CGAAAGGTGA

18751 GGGAGGTGTG ATTAATACAG AGACTCTTAC CAAGGTAAAA CCTAAAACAG
CCCTCCACAC TAATTATGTC TCTGAGAATG GTTCCATTTT GGATTTTGTG

18801 GTCAGGAAAA TGGATGGGAA AAAGATGCTA CAGAAATTTT AGATAAAAAT
CAGTCCTTTT ACCTACCCTT TTTCTACGAT GTCTTAAAAG TCTATTTTAA

18851 GAAATAAGAG TTGGAAATAA TTTTGCCATG GAAATCAATC TAAATGCCAA
CTTTATTCTC AACCTTTATT AAAACGGTAC CTTTAGTTAG ATTTACGGTT

Figure 27T

18951 AGCTAAAGTA CAGTCCTTCC AACGTAAAAA TTTCTGATAA CCAAACACC
TCGATTTTCAT GTCAGGAAGG TTGCATTTTT AAAGACTATT GGGTTTGTGG

19001 TACGACTACA TGAACAAGCG AGTGGTGGCT CCCGGGCTAG TGGACTGCTA
ATGCTGATGT ACTTGTTTCG TCACCACCGA GGGCCCCGATC ACCTGACGAT

19051 CATTAACTTT GGAGCACGCT GGTCCCTTGA CTATATGGAC AACGTCAACC
GTAATTGGAA CCTCGTGCGA CCAGGGAACT GATATACCTG TTGCAGTTGG

19101 CATTTAACCA CCACGCAAT GCTGGCCTGC GCTACCGCTC AATGTTGCTG
GTAAATTGGT GGTGGCGTTA CGACCGGACG CGATGGCGAG TTACAACGAC

19151 GGCAATGGTC GCTATGTGCC CTTCCACATC CAGGTGCCTC AGAAGTTCTT
CCGTTACCAG CGATACACGG GAAGGTGTAG GTCCACGGAG TCTTCAAGAA

19201 TGCCATTAAA AACCTCCTTC TCCTGCCGGG CTCATACACC TACGAGTGGA
ACGGTAATTT TTGGAGGAAG AGGACGGCCC GAGTATGTGG ATGCTCACCT

19251 ACTTCAGGAA GGATGTTAAC ATGGTTCTGC AGAGCTCCCT AGGAAATGAC
TGAAGTCCTT CCTACAATTG TACCAAGACG TCTCGAGGGA TCCTTTACTG

19301 CTAAGGGTTG ACGGAGCCAG CATTAAGTTT GATAGCATTT GCCTTTACGC
GATTCCCAAC TGCCTCGGTC GTAATTCAA CTATCGTAAA CGGAAATGCG

19351 CACCTTCTTC CCCATGGCCC ACAACACCGC CTCCACGCTT GAGGCCATGC
GTGGAAGAAG GGGTACCGGG TGTTGTGGCG GAGGTGCGAA CTCCGGTACG

19401 TTAGAAACGA CACCAACGAC CAGTCCTTTA ACGACTATCT CTCCGCCGCC
AATCTTTGCT GTGGTTGCTG GTCAGGAAAT TGCTGATAGA GAGGCGGCGG

19451 AACATGCTCT ACCCTATACC CGCCAACGCT ACCAACGTGC CCATATCCAT
TTGTACGAGA TGGGATATGG GCGGTTGCGA TGGTTGCACG GGTATAGGTA

19501 CCCCTCCCGC AACTGGGCGG CTTTCCGCGG CTGGGCCTTC ACGCGCCTTA
GGGGAGGGCG TTGACCCGCC GAAAGGCGCC GACCCGGAAG TGCGCGGAAT

19551 AGACTAAGGA AACCCCATCA CTGGGCTCGG GCTACGACCC TTATTACACC
TCTGATTCTT TTGGGGTAGT GACCCGAGCC CGATGCTGGG AATAATGTGG

19601 TACTCTGGCT CTATACCCTA CCTAGATGGA ACCTTTTACC TCAACCACAC
ATGAGACCGA GATATGGGAT GGATCTACCT TGGAAAATGG AGTTGGTGTG

19651 CTTTAAGAAG GTGGCCATTA CCTTTGACTC TTCTGTCAGC TGGCCTGGCA
GAAATTCTTC CACCGGTAAT GGAAACTGAG AAGACAGTCG ACCGGACCGT

19701 ATGACCGCCT GCTTACCCCC AACGAGTTTG AAATTAAGCG CTCAGTTGAC
TACTGGCGGA CGAATGGGGG TTGCTCAAAC TTTAATTGCG GAGTCAACTG

19751 GGGGAGGGTT ACAACGTTGC CCAGTGTAAC ATGACCAAAG ACTGGTTCCT
CCCCTCCCAA TGTTGCAACG GGTCACATTG TACTGGTTTC TGACCAAGGA

19801 GGTACAAATG CTAGCTAACT ATAACATTGG CTACCAGGGC TTCTATATCC
CCATGTTTAC GATCGATTGA TATTGTAACC GATGGTCCCG AAGATATAGG

Figure 274

19851	CAGAGAGCTA GTCTCTCGAT	CAAGGACCGC GTTCTTGGCG	ATGTACTCCT TACATGAGGA	TCTTTAGAAA AGAAATCTTT	CTTCCAGCCC GAAGGTCGGG
19901	ATGAGCCGTC TACTCGGCAG	AGGTGGTGGG TCCACCACCT	TGATACTAAA ACTATGATTT	TACAAGGACT ATGTTCTCTGA	ACCAACAGGT TGGTTGTCCA
19951	GGGCATCCTA CCCGTAGGAT	CACCAACACA GTGGTTGTGT	ACAACTCTGG TGTTGAGACC	ATTTGTTGGC TAAACAACCG	TACCTTGCCC ATGGAACGGG
20001	CCACCATGCG GGTGGTACGC	CGAAGGACAG GCTTCCTGTC	GCCTACCCCTG CGGATGGGAC	CTAACTTCCC GATTGAAGGG	CTATCCGCTT GATAGGCGAA
20051	ATAGGCAAGA TATCCGTTCT	CCGCAGTTGA GGCGTCAACT	CAGCATTACC GTCGTAATGG	CAGAAAAAGT GTCTTTTTCA	TTCTTTGCGA AAGAAACGCT
20101	TCGCACCCCTT AGCGTGGGAA	TGGCGCATCC ACCGCGTAGG	CATTCTCCAG GTAAGAGGTC	TAACTTTATG ATTGAAATAC	TCCATGGGGC AGGTACCCGC
20151	CACTCACAGA GTGAGTGTCT	CCTGGGCCAA GGACCCGGTT	AACCTTCTCT TTGGAAGAGA	ACGCCAACTC TGCGGTTGAG	CGCCCACGCG GCGGGTGCGC
20201	CTAGACATGA GATCTGTACT	CTTTTGAGGT GAAAACCTCCA	GGATCCCATG CCTAGGGTAC	GACGAGCCCA CTGCTCGGGT	CCCTTCTTTA GGGAAGAAAT
20251	TGTTTTGTTT ACAAAACAAA	GAAGTCTTTG CTTCAGAAAC	ACGTGGTCCG TGCACCAGGC	TGTGCACCAG ACACGTGGTC	CCGCACCGCG GGCGTGGCGC
20301	GCGTCATCGA CGCAGTAGCT	AACCGTGTAC TTGGCACATG	CTGCGCACGC GACGCGTGCG	CCTTCTCGGC GGAAGAGCCG	CGGCAACGCC GCCGTTGCGG
20351	ACAACATAAA TGTTGTATTT	GAAGCAAGCA CTTCGTTCGT	ACATCAACAA TGTAATTGTT	CAGCTGCCGC GTCGACGGCG	CATGGGCTCC GTACCCGAGG
20401	AGTGAGCAGG TCACTCGTCC	AACTGAAAGC TTGACTTTTCG	CATTGTCAAA GTAACAGTTT	GATCTTGTTT CTAGAACCAA	GTGGGCCATA CACCCGGTAT
20451	TTTTTTGGGC AAAAAACCCG	ACCTATGACA TGGATACTGT	AGCGCTTTCC TCGCGAAAGG	AGGCTTTGTT TCCGAAACAA	TCTCCACACA AGAGGTGTGT
20501	AGCTCGCCTG TCGAGCGGAC	CGCCATAGTC GCGGTATCAG	AATACGGCCG TTATGCCGGC	GTCGCGAGAC CAGCGCTCTG	TGGGGGCGTA ACCCCCGCAT
20551	CACTGGATGG GTGACCTACC	CCTTTGCCTG GGAAACGGAC	GAACCCGCAC CTTGGGCGTG	TCAAAAACAT AGTTTTTGTA	GCTACCTCTT CGATGGAGAA
20601	TGAGCCCTTT ACTCGGGAAA	GGCTTTTCTG CCGAAAAGAC	ACCAGCGACT TGGTCGCTGA	CAAGCAGGTT GTTCTGTTCA	TACCACTTTG ATGGTCAAAC
20651	AGTACGAGTC TCATGCTCAG	ACTCCTGCGC TGAGGACGCG	CGTAGCGCCA GCATCGCGGT	TTGCTTCTTC AACGAAGAAG	CCCCGACCGC GGGGCTGGCG
20701	TGTATAACGC ACATATTGCG	TGGAAAAGTC ACCTTTTCAG	CACCCAAAGC GTGGGTTTCG	GTACAGGGGC CATGTCCCCG	CCAACTCGGC GGTTGAGCCG
20751	CGCCTGTGGA GCGGACACCT	CTATTCTGCT GATAAGACGA	GCATGTTTCT CGTACAAAGA	CCACGCCTTT GGTGCGGAAA	GCCAACTGGC CGGTTGACCG

Figure 27 V.

20851 CCCAACTCCA TGCTCAACAG TCCCCAGGTA CAGCCCACCC TCGTTCGCAA
GGGTTGAGGT ACGAGTTGTC AGGGGTCCAT GTCGGGTGGG ACGCAGCGTT

20901 CCAGGAACAG CTCTACAGCT TCCTGGAGCG CCACTCGCCC TACTTCCGCA
GGTCCTTGTC GAGATGTCTA AGGACCTCGC GGTGAGCGGG ATGAAGGCGT

20951 GCCACAGTGC GCAGATTAGG AGCGCCACTT CTTTTTGTCA CTTGAAAAAC
CGGTGTCACG CGTCTAATCC TCGCGGTGAA GAAAAACAGT GAACTTTTTG

21001 ATGTAAAAAT AATGTACTAG AGACACTTTC AATAAAGGCA AATGCTTTTA
TACATTTTAA TTACATGATC TCTGTGAAAG TTATTTCCGT TTACGAAAAAT

21051 TTTGTACACT CTCGGGTGAT TATTTACCCC CACCCTTGCC GTCTGCGCCG
AAACATGTGA GAGCCCACTA ATAAATGGGG GTGGGAACGG CAGACGCGGG

21101 TTTAAAAATC AAAGGGGTTC TGCCGCGCAT CGCTATGCGC CACTGGCAGG
AAATTTTTAG TTTCCCAAG ACGGCGCGTA GCGATACGCG GTGACCGTCC

21151 GACACGTTGC GATACTGGTG TTTAGTGCTC CACTTAAACT CAGGCACAAC
CTGTGCAACG CTATGACCAC AAATCACGAG GTGAATTTGA GTCCGTGTTG

21201 CATCCGCGGC AGCTCGGTGA AGTTTTCACT CCACAGGCTG CGCACCATCA
GTAGGCGCCG TCGAGCCACT TCAAAAGTGA GGTGTCCGAC GCGTGGTAGT

21251 CCAACGCGTT TAGCAGGTCG GCGCCGATA TCTTGAAGTC GCAGTTGGGG
GGTTGCGCAA ATCGTCCAGC CCGCGGCTAT AGAACTTCAG CGTCAACCCC

21301 CCTCCGCCCT GCGCGCGCGA GTTGCGATAC ACAGGGTTGC AGCACTGGAA
GGAGGCGGGA CGCGCGCGCT CAACGCTATG TGTCCCAACG TCGTGACCTT

21351 CACTATCAGC GCCGGGTGGT GCACGCTGGC CAGCACGCTC TTGTGCGAGA
GTGATAGTCG CGGCCACCA CGTGCGACCG GTCGTGCGAG AACAGCCTCT

21401 TCAGATCCGC GTCCAGGTCC TCCGCGTTGC TCAGGGCGAA CGGAGTCAAC
AGTCTAGGCG CAGGTCCAGG AGGCGCAACG AGTCCCGCTT GCCTCAGTTG

21451 TTTGGTAGCT GCCTTCCCAA AAAGGGCGCG TGCCCAGGCT TTGAGTTGCA
AAACCATCGA CGGAAGGGTT TTTCCGCGC ACGGGTCCGA AACTCAACGT

21501 CTCGCACCGT AGTGGCATCA AAAGGTGACC GTGCCCAGTC TGGGCGTTAG
GAGCGTGGCA TCACCGTAGT TTTCCACTGG CACGGGCCAG ACCCGCAATC

21551 GATACAGCGC CTGCATAAAA GCCTTGATCT GCTTAAAAGC CACCTGAGCC
CTATGTCGCG GACGTATTTT CGGAACTAGA CGAATTTTCG GTGGACTCGG

21601 TTTGCGCCTT CAGAGAAGAA CATGCCGCAA GACTTGCCCG AAAACTGATT
AAACGCGGAA GTCTCTTCTT GTACGGCGTT CTGAACGGCC TTTTGACTAA

21651 GGCCGGACAG GCCGCGTCGT GCACGCAGCA CCTTGCGTCG GTGTTGGAGA
CCGGCCTGTC CGGCGCAGCA CGTGCGTCGT GGAACGCAGC CACAACCTCT

21701 TCTGCACCAC ATTTGCGCCC CACCGGTTCT TCACGATCTT GGCCTTGCTA
AGACGTGGTG TAAAGCCGGG GTGGCCAAGA AGTGCTAGAA CCGGAACGAT

Figure 27 W

21801 AATCACGTGC TCCTTATTTA TCATAATGCT TCCGTGTAGA CACTTAAGCT
TTAGTGCACG AGGAATAAAT AGTATTACGA AGGCACATCT GTGAATTCTGA

21851 CGCCTTCGAT CTCAGCGCAG CGGTGCAGCC ACAACGCGCA GCCCGTGGGC
GCGGAAGCTA GAGTCGCGTC GCCACGTCGG TGTTCGCGCT CGGGCACCCG

21901 TCGTGATGCT TGTAGGTCAC CTCTGCAAAC GACTGCAGGT ACGCCTGCAG
AGCACTACGA ACATCCAGTG GAGACGTTTG CTGACGTCCA TGCGGACGTC

21951 GAATCGCCCC ATCATCGTCA CAAAGGTCCTT GTTGCTGGTG AAGGTCAGCT
CTTAGCGGGG TAGTAGCAGT GTTTCAGAA CAACGACCAC TTCCAGTCGA

22001 GCAACCCGCG GTGCTCCTCG TTCAGCCAGG TCTTGCCATAC GGCCGCCAGA
CGTTGGGCGC CACGAGGAGC AAGTCGGTCC AGAACGTATG CCGGCGGTCT

22051 GCTTCCACTT GGTCAGGCAG TAGTTTGAAG TTCGCCTTTA GATCGTTATC
CGAAGGTGAA CCAGTCCGTC ATCAAAC TTC AAGCGGAAAT CTAGCAATAG

22101 CACGTGGTAC TTGTCCATCA GCGCGCGCGC AGCCTCCATG CCCTTCTCCC
GTGCACCATG AACAGGTAGT CGCGCGCGCG TCGGAGGTAC GGAAGAGGG

22151 ACGCAGACAC GATCGGCACA CTCAGCGGGT TCATCACCGT AATTTCACTT
TGCGTCTGTG CTAGCCGTGT GAGTCGCCCA AGTAGTGGCA TTAAAGTGAA

22201 TCCGCTTCGC TGGGCTCTTC CTCTTCCTCT TCGGTCCGCA TACCACGCGC
AGGCGAAGCG ACCCGAGAAG GAGAAGGAGA ACGCAGGCGT ATGGTGC GCG

22251 CACTGGGTCTG TCTTCATTCA GCCGCCGCAC TGTGCGCTTA CCTCCTTTGC
GTGACCCAGC AGAAGTAAGT CGGCGGCGTG ACACGCGAAT GGAGGAAACG

22301 CATGCTTGAT TAGCACCAGT GGGTTGCTGA AACCACCAT TTGTAGCGCC
GTACGAATA ATCGTGGCCA CCCAACGACT TTGGGTGGTA AACATCGCGG

22351 ACATCTTCTC TTTCTTCCTC GCTGTCCACG ATTACCTCTG GTGATGGCGG
TGTAAGAG AAAGAAGGAG CGACAGGTGC TAATGGAGAC CACTACCGCC

22401 GCGCTCGGGC TTGGGAGAAG GCGGCTTCTT TTTCTTCTTG GCGCAATGG
CGCGAGCCCG AACCTCTTC CCGGAAGAA AAAGAAGAAC CCGCTTACC

22451 CCAAATCCGC CGCCGAGGTC GATGGCCGCG GGCTGGGTGT GCGCGGCACC
GGTTTAGGCG GCGGCTCCAG CTACCGGCGC CCGACCCACA CGCGCCGTGG

22501 AGCGCGTCTT GTGATGAGTC TTCTCGTCC TCGGACTCGA TACGCCGCCT
TCGCGCAGAA CACTACTCAG AAGGAGCAGG AGCCTGAGCT ATGCGGCGGA

22551 CATCCGCTTT TTTGGGGGCG CCCGGGGAGG CGGCGGCGAC GGGGACGGGG
GTAGGCGAAA AAACCCCGC GGGCCCCCTC GCGGCGCTG CCCCTGCCCC

22601 ACGACACGTC CTCCATGGTT GGGGGACGTC GCGCCGCACC GCGTCCGCGC
TGCTGTGAG GAGGTACCAA CCCCCTGCAG CGCGGCGTGG CGCAGGCGCG

22651 TCGGGGGTGG TTTGCGGCTG CTCTCTTCC CGACTGGCCA TTTCTTCTC
AGCCCCACC AAAGCGCGAC GAGGAGAAGG GCTGACCGGT AAAGGAAGAG

Figure 27 X

22751 CCGCCCCCTC TGAGTTCGCC ACCACCGCCT CCACCGATGC CGCCAACGCG
GGCGGGGGAG ACTCAAGCGG TGGTGGCGGA GGTGGCTACG GCGGTTGCGC

22801 CCTACCACCT TCCCCGTCGA GGCACCCCG CTTGAGGAGG AGGAAGTGAT
GGATGGTGGA AGGGGCAGCT CCGTGGGGGC GAACTCCTCC TCCTTCACTA

22851 TATCGAGCAG GACCCAGGTT TTGTAAGCGA AGACGACGAG GACCGCTCAG
ATAGCTCGTC CTGGGTCCAA AACATTGCT TCTGCTGCTC CTGGCGAGTC

22901 TACCAACAGA GGATAAAAAG CAAGACCAGG ACAACGCAGA GGCAAACGAG
ATGGTTGTCT CCTATTTTTT GTTCTGGTCC TGTTGCGTCT CCGTTTGCTC

22951 GAACAAGTCG GCGGGGGGGA CGAAAGGCAT GCGCACTACC TAGATGTGGG
CTTGTTACAG CCGCCCCCT GCTTTCCGTA CCGCTGATGG ATCTACACCC

23001 AGACGACGTG CTGTTGAAGC ATCTGCAGCG CCAGTGCGCC ATTATCTGCG
TCTGCTGCAC GACAACTTCG TAGACGTGCG GGTCAAGCGG TAATAGACGC

23051 ACGCGTTGCA AGAGCGCAGC GATGTGCCCC TCGCCATAGC GGATGTCAGC
TGCGCAACGT TCTCGCGTCG CTACACGGGG AGCGGTATCG CCTACAGTCG

23101 CTTGCCTACG AACGCCACCT ATTCTCACCG CGCGTACCCC CCAAACGCCA
GAACGGATGC TTGCGGTGGA TAAGAGTGGC GCGCATGGGG GGTTCGCGGT

23151 AGAAAACGGC ACATGCGAGC CCAACCCGCG CCTCAACTTC TACCCCGTAT
TCTTTTGCCG TGTACGCTCG GGTGGGCGC GGAGTTGAAG ATGGGGCATA

23201 TTGCCGTGCC AGAGGTGCTT GCCACCTATC ACATCTTTTT CCAAACCTGC
AACGGCACGG TCTCCACGAA CCGTGGATAG TGTAGAAAAA GGTTCGACG

23251 AAGATACCCC TATCCTGCCG TGCCAACCGC AGCCGAGCGG ACAAGCAGCT
TTCTATGGGG ATAGGACGGC ACGGTTGGCG TCGGCTCGCC TGTTGCTCGA

23301 GGCCTTGCGG CAGGGCGCTG TCATACCTGA TATCGCCTCG CTCAACGAAG
CCGGAACGCC GTCCCGCGAC AGTATGGACT ATAGCGGAGC GAGTTGCTTC

23351 TGCCAAAAAT CTTTGAGGGT CTTGGACGCG ACGAGAAGCG CGCGGCAAAC
ACGGTTTTTA GAAACTCCCA GAACCTGCGC TGCTCTTCGC GCGCCGTTTG

23401 GCTCTGCAAC AGGAAAACAG CGAAAATGAA AGTCACTCTG GAGTGTGGT
CGAGACGTTG TCCTTTTGTC GCTTTTACTT TCAGTGAGAC CTCACAACCA

23451 GGAACCTCGAG GGTGACAACG CGCGCCTAGC CGTACTAAAA CGCAGCATCG
CCTTGAGCTC CCACTGTTGC GCGCGGATCG GCATGATTTT GCGTCGTAGC

23501 AGGTCAACCA CTTTGCCCTAC CCGGCACTTA ACCTACCCCC CAAGGTCATG
TCCAGTGGGT GAAACGGATG GGCCGTGAAT TGGATGGGGG GTTCCAGTAC

23551 AGCACAGTCA TGAGTGAGCT GATCGTGCGC CGTGCGCAGC CCCTGGAGAG
TCGTGTCAGT ACTCACTCGA CTAGCACGCG GCACGCGTCG GGGACCTCTC

23601 GGATGCAAAT TTGCAAGAAC AAACAGAGGA GGGCCTACCC GCAGTTGGCG
CCTACGTTTA AACGTTCTTG TTTGTCTCCT CCCGGATGGG CGTCAACCGC

Figure 27 Y

23701 GAGCGACGCA AACTAATGAT GGCCGCAGTG CTCGTTACCG TGGAGCTTGA
CTCGCTGCGT TTGATTACTA CCGGCGTCAC GAGCAATGGC ACCTCGAACT

23751 GTGCATGCAG CGGTTCTTTG CTGACCCGGA GATGCAGCGC AAGCTAGAGG
CACGTACGTC GCCAAGAAAC GACTGGGCCT CTACGTCGCG TTCGATCTCC

23801 AAACATTGCA CTACACCTTT CGACAGGGCT ACGTACGCCA GGCTTGCAAG
TTTGTAACGT GATGTGAAA GCTGTCCCGA TGCATGCGGT CCGGACGTTT

23851 ATCTCCAACG TGGAGCTCTG CAACCTGGTC TCCTACCTTG GAATTTTGA
TAGAGGTTGC ACCTCGAGAC GTTGGACCAG AGGATGGAAC CTTAAAACGT

23901 CGAAAACCGC CTTGGGCAAA ACGTGCTTCA TTCCACGCTC AAGGGCGAGG
GCTTTTGGCG GAACCCGTTT TGCACGAAGT AAGGTGCGAG TTCCCGCTCC

23951 CGCGCCGCGA CTACGTCCGC GACTGCGTTT ACTTATTTCT ATGCTACACC
GCGCGGCGCT GATGCAGGCG CTGACGCAAA TGAATAAAGA TACGATGTGG

24001 TGGCAGACGG CCATGGGCGT TTGGCAGCAG TGCTTGAGG AGTGCAACCT
ACCGTCTGCC GGTACCCGCA AACCCTCGTC ACGAACCTCC TCACGTTGGA

24051 CAAGGAGCTG CAGAACTGC TAAAGCAAAA CTTGAAGGAC CTATGGACGG
GTTCTTCGAC GTCTTTGACG ATTTCTGTTT GAACCTCCTG GATACCTGCC

24101 CCTTCAACGA GCGCTCCGTG GCCGCGCACC TGGCGGACAT CATTTTCCCC
GGAAGTTGCT CGCGAGGCAC CGGCGCGTGG ACCGCCTGTA GTAAAAGGGG

24151 GAACGCCTGC TTAAAACCCT GCAACAGGGT CTGCCAGACT TCACCAGTCA
CTTGCGGACG AATTTTGGGA CGTTGTCCCA GACGGTCTGA AGTGGTCAGT

24201 AAGCATGTTG CAGAACTTTA GGAACCTTAT CCTAGAGCGC TCAGGAATCT
TTCGTACAAC GTCTTGAAAT CCTTGAAATA GGATCTCGCG AGTCCTTAGA

24251 TGCCCGCCAC CTGCTGTGCA CTTCTAGCG ACTTTGTGCC CATTAAGTAC
ACGGGCGGTG GACGACACGT GAAGGATCGC TGAAACACGG GTAATTCATG

24301 CGCGAATGCC CTCCGCCGCT TTGGGGCCAC TGCTACCTTC TGCAGCTAGC
GCGCTTACGG GAGGCGGCGA AACCCCGGTG ACGATGGAAG ACGTCGATCG

24351 CAACTACCTT GCCTACCACT CTGACATAAT GGAAGACGTG AGCGGTGACG
GTTGATGGAA CGGATGGTGA GACTGTATTA CCTTCTGCAC TCGCCACTGC

24401 GTCTACTGGA GTGTCACTGT CGCTGCAACC TATGCACCCC GCACCGCTCC
CAGATGACCT CACAGTGACA GCGACGTTGG ATACGTGGGG CGTGGCGAGG

24451 CTGGTTTGA ATTGCGAGCT GCTTAACGAA AGTCAAATTA TCGGTACCTT
GACCAAACGT TAAGCGTCGA CGAATTGCTT TCAGTTTAAAT AGCCATGGAA

24501 TGAGCTGCAG GGTCCCTCGC CTGACGAAAA GTCCGCGGCT CCGGGGTTGA
ACTCGACGTC CCAGGGAGCG GACTGCTTTT CAGGCGCCGA GGCCCCAACT

24551 AACTCACTCC GGGGCTGTGG ACGTCGGCTT ACCTTCGCAA ATTTGTACCT
TTGAGTGAGG CCCCACACC TGCAGCCGAA TGGAAGCGTT TAAACATGGA

Figure 272

24601 GAGGACTACC ACGCCCACGA GATTAGGTTC TACGAAGACC AATCCCCGCC
CTCCTGATGG TCGGGGTGCT CTAATCCAAG ATGCTTCTGG TTAGGGCGGG

24651 GCCTAATGCG GAGCTTACCG CCTGCGTCAT TACCCAGGGC CACATTCTTG
CGGATTACGC CTCGAATGGC GGACGCAGTA ATGGGTCCCG GTGTAAGAAC

24701 GCCAATTGCA AGCCATCAAC AAAGCCCGCC AAGAGTTTCT GCTACGAAAG
CGGTTAACGT TCGGTAGTTG TTTCGGGCGG TTCTCAAAGA CGATGCTTTC

24751 GGACGGGGGG TTTACTTGGA CCCCCAGTCC GCGGAGGAGC TCAACCCAAT
CCTGCCCCCC AAATGAACCT GGGGGTCAGG CCGCTCCTCG AGTTGGGTTA

24801 CCCCCCGCCG CCGCAGCCCT ATCAGCAGCA GCCGCGGGCC CTTGCTTCCC
GGGGGGCGGC GGCCTCGGGA TAGTCGTCGT CCGCGCCCGG GAACGAAGGG

24851 AGGATGGCAC CCAAAAAGAA GCTGCAGCTG CCGCCGCCAC CCACGGACGA
TCCTACCGTG GGTTTTCTT CGACGTCGAC GCGGCGGGTG GGTGCCTGCT

24901 GGAGGAATAC TGGGACAGTC AGGCAGAGGA GGTTTTGGAC GAGGAGGAGG
CCTCCTTATG ACCCTGTCAG TCCGTCTCCT CCAAAACCTG CTCCTCCTCC

24951 AGGACATGAT GGAAGACTGG GAGAGCCTAG ACGAGGAAGC TTCCGAGGTC
TCCTGTACTA CCTTCTGACC CTCTCGGATC TGCTCCTTCG AAGGCTCCAG

25001 GAAGAGGTGT CAGACGAAAC ACCGTCACCC TCGGTTCGAT TCCCCTCGCC
CTTCTCCACA GTCTGCTTTG TGGCAGTGGG AGCCAGCGTA AGGGGAGCGG

25051 GCGCGCCCGC AAATCGGCAA CCGGTTCAG CATGGCTACA ACCTCCGCTC
CCGCGGGGTC TTTAGCCGTT GGCCAAGGTC GTACCGATGT TGGAGGCGAG

25101 CTCAGGCGCC GCCGGCACTG CCCGTTCGCC GACCCAACCG TAGATGGGAC
GAGTCCGCGG CCGCCGTGAC GGGCAAGCGG CTGGGTGGC ATCTACCCTG

25151 ACCACTGGAA CCAGGGCCGG TAAGTCCAAG CAGCCGCCGC CGTTAGCCCA
TGGTGACCTT GGTCCCGGCC ATTCAAGGTC GTCGGCGGCG GCAATCGGGT

25201 AGAGCAACAA CAGCGCCAAG GCTACCGCTC ATGGCGCGGG CACAAGAACG
TCTCGTTGTT GTCGCGGTTT CGATGGCGAG TACCGCGCCC GTGTTCTTGC

25251 CCATAGTTGC TTGCTTGCAA GACTGTGGGG GCAACATCTC CTTCCGCCGC
GGTATCAACG AACGAACGTT CTGACACCCC CGTTGTAGAG GAAGCGGGCG

25301 CGCTTTCTTC TCTACCATCA CCGCGTGGCC TTCCCCCGTA ACATCCTGCA
GCGAAAGAAG AGATGGTAGT GCCGCACCGG AAGGGGGCAT TGTAGGACGT

25351 TTACTIONCGT CATCTCTACA GCCCATACTG CACCGGCGGC AGCGGCAGCA
AATGATGGCA GTAGAGATGT CGGGTATGAC GTGGCCGCCG TCGCCGTCGT

25401 ACAGCAGCGG CCACACAGAA GCAAAGGCGA CCGGATAGCA AGACTCTGAC
TGTCGTCGCC GGTGTGTCTT CGTTTCCGCT GGCCTATCGT TCTGAGACTG

25451 AAAGCCCAAG AAATCCACAG CCGCGGCAGC AGCAGGAGGA GGAGCGCTGC
TTTCGGGTTT TTTAGGTGTC GCCGCCGTCG TCGTCTCTCT CCTCGCGACG

25501 GTCTGGCGCC CAACGAACCC GTATCGACCC GCGAGCTTAG AAACAGGATT
CAGACCGCGG GTTGCTTGGG CATAGCTGGG CGCTCGAATC TTTGTCCTAA

Figure 27 AA

25551	TTTCCCACAC	TGTATGCTAT	ATTTC AACAG	AGCAGGGG	AAGAACAAGA
	AAAGGGTGAG	ACATACGATA	TAAAGTTGTC	TCGTCCCCCG	TTCTTGTCT
25601	GCTGAAAATA	AAAAACAGGT	CTCTGCGATC	CCTCACCCGC	AGCTGCCTGT
	CGACTTTTAT	TTTTTGTTCA	GAGACGCTAG	GGAGTGGGCG	TCGACGGACA
25651	ATCACAAAAG	CGAAGATCAG	CTTCGGCGCA	CGCTGGAAGA	CGCGGAGGCT
	TAGTGTTTTC	GCTTCTAGTC	GAAGCCGCGT	GCGACCTTCT	GCGCCTCCGA
25701	CTCTTCAGTA	AATACTGCGC	GCTGACTCTT	AAGGACTAGT	TTCGCGCCCT
	GAGAAGTCAT	TTATGACGCG	CGACTGAGAA	TTCTTGATCA	AAGCGCGGGA
25751	TTCTCAAATT	TAAGCGCGAA	AACTACGTCA	TCTCCAGCGG	CCACACCCCG
	AAGAGTTTAA	ATTCGCGCTT	TTGATGCAGT	AGAGGTGCGC	GGTGTGGGCC
25801	CGCCAGCACC	TGTTGTTCAGC	GCCATTATGA	GCAAGGAAAT	TCCCACGCCC
	GCGGTGCTGG	ACAACAGTCG	CGGTAATACT	CGTTCTTTTA	AGGGTGCGGG
25851	TACATGTGGA	GTTACCAGCC	ACAAATGGGA	CTTGCGGCTG	GAGCTGCCCA
	ATGTACACCT	CAATGGTTCG	TGTTTACCCT	GAACGCCGAC	CTCGACGGGT
25901	AGACTACTCA	ACCCGAATAA	ACTACATGAG	CGCGGGACCC	CACATGATAT
	TCTGATGAGT	TGGGCTTATT	TGATGTACTC	GCGCCCTGGG	GTGTACTATA
25951	CCCGGGTCAA	CGGAATACGC	GCCCACCGAA	ACCGAATTCT	CCTGGAACAG
	GGGCCCAGTT	GCCTTATGCG	CGGGTGGCTT	TGGCTTAAGA	GGACCTTGTC
26001	GCGGCTATTA	CCACCACACC	TCGTAATAAC	CTTAATCCCC	GTAGTTGGCC
	CGCCGATAAT	GGTGGTGTGG	AGCATTATTG	GAATTAGGGG	CATCAACCGG
26051	CGCTGCCCTG	GTGTACCAGG	AAAGTCCCGC	TCCCACCACT	GTGGTACTTC
	GCGACGGGAC	CACATGGTCC	TTTCAGGGCG	AGGGTGGTGA	CACCATGAAG
26101	CCAGAGACGC	CCAGGCCGAA	GTTCAGATGA	CTAACTCAGG	GGCGCAGCTT
	GGTCTCTGCG	GGTCCGGCTT	CAAGTCTACT	GATTGAGTCC	CCGCGTCGAA
26151	GCGGGCGGCT	TTCGTACACAG	GGTGCGGTCT	CCCGGGCAGG	GTATAACTCA
	CGCCCGCCGA	AAGCAGTGTC	CCACGCCAGC	GGGCCCGTCC	CATATTGAGT
26201	CCTGACAATC	AGAGGGCGAG	GTTTCAGCT	CAACGACGAG	TCGGTGAGCT
	GGACTGTTAG	TCTCCCGCTC	CATAAGTCGA	GTTGCTGCTC	AGCCACTCGA
26251	CCTCGCTTGG	TCTCCGTCCG	GACGGGACAT	TTCAGATCGG	CGGCGCCGGC
	GGAGCGAACC	AGAGGCAGGC	CTGCCCTGTA	AAGTCTAGCC	GCCGCGGCCG
26301	CGCTCTTCAT	TCACGCCTCG	TCAGGCAATC	CTAACTCTGC	AGACCTCGTC
	GCGAGAAGTA	AGTGCGGAGC	AGTCCGTTAG	GATTGAGACG	TCTGGAGCAG
26351	CTCTGAGCCG	CGCTCTGGAG	GCAATTGGAAC	TCTGCAATTT	ATTGAGGAGT
	GAGACTCGGC	GCGAGACCTC	CGTAACCTTG	AGACGTTAAA	TAACCTCTCA
26401	TTGTGCCATC	GGTCTACTTT	AACCCCTTCT	CGGGACCTCC	CGGCCACTAT
	AACACGGTAG	CCAGATGAAA	TTGGGGAAGA	GCCCTGGAGG	GCCGGTGATA
26451	CCGGATCAAT	TTATTCCCTAA	CTTTGACGCG	GTAAAGGACT	CGGCGGACGG
	GGCCTAGTTA	AATAAGGATT	GAAACTGCGC	CATTTCTTGA	GCCGCCTGCC

Figure 27 AB

26501 CTACGACTGA ATGTTAAGTG GAGAGGCAGA GCAACTGCGC CTGAAACACC
GATGCTGACT TACAATTACAC CTCCTCCGTCT CGTTGACGCG GACTTTGTGG

26551 TGGTCCACTG TCGCCGCCAC AAGTGCCTTG CCCGCGACTC CGGTGAGTTT
ACCAGGTGAC AGCGGCGGTG TTCACGAAAC GGGCGCTGAG GCCACTCAAA

26601 TGCTACTTTG AATTGCCCGA GGATCATATC GAGGGCCCGG CGCACGGCGT
ACGATGAAAC TTAACGGGCT CCTAGTATAG CTCCCGGGCC GCGTGCCGCA

26651 CCGGCTTACC GCCCAGGGAG AGCTTGCCCG TAGCCTGATT CGGGAGTTTA
GGCCGAATGG CGGGTCCCTC TCGAACGGGC ATCGGACTAA GCCCTCAAAT

26701 CCCAGCGCCC CCTGCTAGTT GAGCGGGACA GGGGACCCTG TGTTCCTACT
GGGTGCGGGG GGACGATCAA CTCGCCCTGT CCCCTGGGAC ACAAGAGTGA

26751 GTGATTTGCA ACTGTCCTAA CCCTGGATTA CATCAAGATC TTTGTTGCCA
CACTAAACGT TGACAGGATT GGGACCTAAT GTAGTTCTAG AAACAACGGT

26801 TCTCTGTGCT GAGTATAATA AATACAGAAA TTAAATATA CTGGGGCTCC
AGAGACACGA CTCATATTAT TTATGTCTTT AATTTTATAT GACCCCGAGG

26851 TATCGCCATC CTGTAAACGC CACCGTCTTC ACCCGCCCAA GCAAACCAAG
ATAGCGGTAG GACATTTGCG GTGGCAGAAG TGGGCGGGTT CGTTTGTTTC

26901 GCGAACCTTA CCTGGTACTT TTAACATCTC TCCCTCTGTG ATTTACAACA
CGCTTGGAAT GGACCATGAA AATTGTAGAG AGGGAGACAC TAAATGTTGT

26951 GTTTC AACCC AGACGGAGTG AGTCTACGAG AGAACCTCTC CGAGCTCAGC
CAAAGTTGGG TCTGCCTCAC TCAGATGCTC TCTTGAGAG GCTCGAGTCG

27001 TACTCCATCA GAAAAACAC CACCCTCCTT ACCTGCCGGG AACGTACGAG
ATGAGGTAGT CTTTTTTGTG GTGGGAGGAA TGGACGGCCC TTGCATGCTC

27051 TGCCTCACCG GCCGCTGCAC CACACCTACC GCCTGACCGT AAACCAGACT
ACGCAGTGGC CGGCGACGTG GTGTGGATGG CGGACTGGCA TTTGGTCTGA

27101 TTTTCCGGAC AGACCTCAAT AACTCTGTTT ACCAGAACAG GAGGTGAGCT
AAAAGGCCTG TCTGGAGTTA TTGAGACAAA TGGTCTTGTC CTCCACTCGA

27151 TAGAAAACCC TTAGGGTATT AGGCCAAAGG CGCAGCTACT GTGGGGTTTA
ATCTTTTGGG AATCCCATAA TCCGGTTTCC GCGTCGATGA CACCCCAAAT

27201 TGAACAATTC AAGCAACTCT ACGGGCTATT CTAATTCAGG TTTCTCTAGA
ACTTGTTAAG TTCGTTGAGA TGCCCGATAA GATTAAGTCC AAAGAGATCT

27251 ATCGGGGTTG GGGTTATTCT CTGTCTTG TG ATTCTCTTTA TTCTTATACT
TAGCCCCAAC CCCAATAAGA GACAGAACAC TAAGAGAAAT AAGAATATGA

27301 AACGCTTCTC TGCCTAAGGC TCGCCGCTG CTGTGTGCAC ATTTGCATTT
TTGCGAAGAG ACGGATTCCG AGCGGCGGAC GACACACGTG TAAACGTAAA

27351 ATTGTCAGCT TTTTAAACGC TGGGGTCGCC ACCCAAGATG ATTAGGTACA
TAACAGTCGA AAAATTTGCG ACCCCAGCGG TGGGTTCTAC TAATCCATGT

27401 TAATCCTAGG TTTACTCACC CTTGCGTCAG CCCACGGTAC CACCCAAAAG
ATTAGGATCC AAATGAGTGG GAACGCAGTC GGGTGCCATG GTGGGTTTTC

Figure 27 AC

27451	GTGGATTT	AGGAGCCAGC	CTGTAATGTT	ACATTTCGCA	CTGAAGCTAA
	CACCTAAAAT	TCCTCGGTCG	GACATTACAA	TGTAAGCGTC	GACTTCGATT
27501	TGAGTGCACC	ACTCTTATAA	AATGCACCAC	AGAACATGAA	AAGCTGCTTA
	ACTCACGTGG	TGAGAATATT	TTACGTGGTG	TCTTGTACTT	TTCGACGAAT
27551	TTCGCCACAA	AAACAAAATT	GGCAAGTATG	CTGTTTATGC	TATTTGGCAG
	AAGCGGTGTT	TTTGTTTTAA	CCGTTTCATC	GACAAATACG	ATAAACCGTC
27601	CCAGGTGACA	CTACAGAGTA	TAATGTTACA	GTTTTCCAGG	GTAAAAGTCA
	GGTCCACTGT	GATGTCTCAT	ATTACAATGT	CAAAAGGTCC	CATTTTCAGT
27651	TAAAACTTTT	ATGTATACTT	TTCCATTTTA	TGAAATGTGC	GACATTACCA
	ATTTTGAAAA	TACATATGAA	AAGGTAAAA	ACTTTACACG	CTGTAATGGT
27701	TGTACATGAG	CAAACAGTAT	AAGTTGTGGC	CCCCACAAAA	TTGTGTGGAA
	ACATGTACTC	GTTTGTCTATA	TTCAACACCG	GGGGTGTTTT	AACACACCTT
27751	AACACTGGCA	CTTCTGCTG	CACTGCTATG	CTAATTACAG	TGCTCGCTTT
	TTGTGACCGT	GAAAGACGAC	GTGACGATAC	GATTAATGTC	ACGAGCGAAA
27801	GGTCTGTACC	CTACTCTATA	TTAAATACAA	AAGCAGACGC	AGCTTTATTG
	CCAGACATGG	GATGAGATAT	AATTTATGTT	TTCGTCTGCG	TCGAAATAAC
27851	AGGAAAAGAA	AATGCCTTAA	TTTACTAAGT	TACAAAGCTA	ATGTCACCAC
	TCCTTTTCTT	TTACGGAATT	AAATGATTCA	ATGTTTCGAT	TACAGTGGTG
27901	TAAGTCTTTT	ACTCGCTGCT	TGCAAAACAA	ATTCAAAAAG	TTAGCATTAT
	ATTGACGAAA	TGAGCGACGA	ACGTTTTGTT	TAAGTTTTTC	AATCGTAATA
27951	AATTAGAATA	GGATTTAAAC	CCCCCGGTCA	TTTCCTGCTC	AATACCATTG
	TTAATCTTAT	CCTAAATTTG	GGGGGCCAGT	AAAGGACGAG	TTATGGTAAG
28001	CCCTGAACAA	TTGACTCTAT	GTGGGATATG	CTCCAGCGCT	ACAACCTTGA
	GGGACTTGTT	AACTGAGATA	CACCCTATAC	GAGGTCGCGA	TGTTGGAAC
28051	AGTCAGGCTT	CCTGGATGTC	AGCATCTGAC	TTTGGCCAGC	ACCTGTCCCG
	TCAGTCCGAA	GGACCTACAG	TCGTAGACTG	AAACCGGTCG	TGGACAGGGC
28101	CGGATTTGTT	CCAGTCCAAC	TACAGCGACC	CACCCTAACA	GAGATGACCA
	GCCTAAACAA	GGTCAGGTTG	ATGTCGCTGG	GTGGGATTGT	CTCTACTGGT
28151	ACACAACCAA	CGCGGCCGCC	GCTACCGGAC	TTACATCTAC	CACAAATACA
	TGTGTTGGTT	GCGCCGGCGG	CGATGGCCTG	AATGTAGATG	GTGTTTATGT
28201	CCCCAAGTTT	CTGCCTTTGT	CAATAACTGG	GATAACTTGG	GCATGTGGTG
	GGGGTTCAAA	GACGGAAACA	GTTATTGACC	CTATTGAACC	CGTACACCAC
28251	GTTCTCCATA	GCGCTTATGT	TTGTATGCCT	TATTATTATG	TGGCTCATCT
	CAAGAGGTAT	CGCGAATACA	AACATACGGA	ATAATAATAC	ACCGAGTAGA
28301	GCTGCCTAAA	GCGCAAACGC	GCCCCGACCAC	CCATCTATAG	TCCCATCATT
	CGACGGATTT	CGCGTTTGCG	CGGGCTGGTG	GGTAGATATC	AGGGTAGTAA
28351	GTGCTACACC	CAAACAATGA	TGGAATCCAT	AGATTGGACG	GACTGAAACA
	CACGATGTGG	GTTTGTTACT	ACCTTAGGTA	TCTAACCTGC	CTGACTTTGT

Figure 27A D

28451 TTTTATATTA CTGACCCTTG TTGCGCTTTT TTGTGCGTGC TCCACATTGG
 AAAATATAAT GACTGGGAAC AACGCGAAAA AACACGCACG AGGTGTAACC
 28501 CTGCGGTTTC TCACATCGAA GTAGACTGCA TTCCAGCCTT CACAGTCTAT
 GACGCCAAAG AGTGTAGCTT CATCTGACGT AAGGTCGGAA GTGTCAGATA
 28551 TTGCTTTACG GATTTGTCAC CCTCACGCTC ATCTGCAGCC TCATCACTGT
 AACGAAATGC CTAAACAGTG GGAGTGCAG TAGACGTCGG AGTAGTGACA
 28601 GGTTCATCGCC TTTATCCAGT GCATTGACTG GGTCTGTGTG CGCTTTGCAT
 CCAGTAGCGG AAATAGGTCA CGTAACTGAC CCAGACACAC GCGAAACGTA
 28651 ATCTCAGACA CCATCCCCAG TACAGGGACA GGACTATAGC TGAGCTTCTT
 TAGAGTCTGT GGTAGGGGTC ATGTCCCTGT CCTGATATCG ACTCGAAGAA
 28701 AGAATTCTTT AATTATGAAA TTTACTGTGA CTTTCTGTCT GATTATTTGC
 TCTTAAGAAA TTAATACTTT AAATGACACT GAAAAGACGA CTAATAAACG
 28751 ACCCTATCTG CGTTTTGTTT CCCGACCTCC AAGCCTCAA GACATATATC
 TGGGATAGAC GCAAAACAAG GGGCTGGAGG TTCGGAGTTT CTGTATATAG
 28801 ATGCAGATTC ACTCGTATAT GGAATATTCC AAGTTGCTAC AATGAAAAAA
 TACGTCTAAG TGAGCATATA CCTTATAAGG TTCAACGATG TTACTTTTTT
 28851 GCGATCTTTC CGAAGCCTGG TTATATGCAA TCATCTCTGT TATGGTGTTC
 CGCTAGAAAG GCTTCGGACC AATATACGTT AGTAGAGACA ATACCACAAG
 28901 TGCAGTACCA TCTTAGCCCT AGCTATATAT CCCTACCTTG ACATTGGCTG
 ACGTCATGGT AGAATCGGGA TCGATATATA GGGATGGAAC TGTAACCGAC
 28951 GAACGCAATA GATGCCATGA ACCACCCAAC TTTCCCCGCG CCCGCTATGC
 CTTGCGTTAT CTACGGTACT TGGTGGGTG AAAGGGGCGC GGGCGATACG
 29001 TTCCACTGCA ACAAGTTGTT GCCGGCGGCT TTGTCCCAGC CAATCAGCCT
 AAGGTGACGT TGTTCAACAA CGGCCGCCGA AACAGGGTCG GTTAGTCGGA
 29051 CGCCACCTT CTCCCACCCC CACTGAAATC AGCTACTTTA ATCTAACAGG
 GCGGGTGGAA GAGGGTGGGG GTGACTTTAG TCGATGAAAT TAGATTGTCC
 29101 AGGAGATGAC TGACACCCTA GATCTAGAAA TGGACGGAAT TATTACAGAG
 TCCTCTACTG ACTGTGGGAT CTAGATCTTT ACCTGCCCTA ATAATGTCTC
 29151 CAGCGCCTGC TAGAAAGACG CAGGGCAGCG GCCGAGCAAC AGCGCATGAA
 GTCGCGGACG ATCTTTCTGC GTCCCGTCGC CGGCTCGTTG TCGCGTACTT
 29201 TCAAGAGCTC CAAGACATGG TTAAC TTGCA CCAGTGCAAA AGGGGTATCT
 AGTTCTCGAG GTTCTGTACC AATTGAACGT GGTACGTTT TCCCCATAGA
 29251 TTTGTCTCGT AAAGCAGGCC AAAGTCACCT ACGACAGTAA TACCACCGGA
 AAACAGAGCA TTTCGTCCGG TTTCAGTGGA TGCTGTCATT ATGGTGGCCT
 29301 CACCGCCTTA GCTACAAGTT GCCAACCAAG CGTCAGAAAT TGGTGGTCAT
 GTGGCGGAAT CGATGTTCAA CGGTGGGTTC GCAGTCTTTA ACCACCAGTA

Figure 27AE

29401 GCTGCATTCA CTCACCTTGT CAAGGACCTG AGGATCTCTG CACCCTTATT
CGACGTAAGT GAGTGGAAACA GTTCCTGGAC TCCTAGAGAC GTGGGAATAA

29451 AAGACCCTGT GCGGTCTCAA AGATCTTATT CCCTTTAACT AATAAAAAAA
TTCTGGGACA CGCCAGAGTT TCTAGAATAA GGGAAATTGA TTATTTT

29501 AATAATAAAG CATCACTTAC TTAAATCAG TTAGCAAATT TCTGTCCAGT
TTATTATTTT GTAGTGAATG AATTTTAGTC AATCGTTTAA AGACAGGTCA

29551 TTATTCAGCA GCACCTCCTT GCCCTCCTCC CAGCTCTGGT ATTGCAGCTT
AATAAGTCGT CGTGGAGGAA CGGGAGGAGG GTCGAGACCA TAACGTCGAA

29601 CCTCCTGGCT GCAAACCTTC TCCACAATCT AAATGGAATG TCAGTTTCCT
GGAGGACCGA CGTTTGAAAG AGGTGTTAGA TTTACCTTAC AGTCAAAGGA

29651 CCTGTTCTCTG TCCATCCGCA CCCACTATCT TCATGTTGTT GCAGATGAAG
GGACAAGGAC AGGTAGGCGT GGGTGATAGA AGTACAACAA CGTCTACTTC

29701 CGCGCAAGAC CGTCTGAAGA TACCTTCAAC CCCGTGTATC CATATGACAC
GCGCGTTCTG GCAGACTTCT ATGGAAGTTG GGGCACATAG GTATACTGTG

29751 GGAAACCGGT CCTCCAACCTG TGCCTTTTCT TACTCCTCCC TTTGTATCCC
CCTTTGGCCA GGAGGTTGAC ACGGAAAAGA ATGAGGAGGG AAACATAGGG

29801 CCAATGGGTT TCAAGAGAGT CCCCCTGGGG TACTCTCTTT GCGCCTATCC
GGTTACCCAA AGTTCTCTCA GGGGGACCCC ATGAGAGAAA CGCGGATAGG

29851 GAACCTCTAG TTACCTCCAA TGGCATGCTT GCGCTCAAAA TGGGCAACGG
CTTGAGATC AATGGAGGTT ACCGTACGAA CGCGAGTTTT ACCCGTTGCC

29901 CCTCTCTCTG GACGAGGCCG GCAACCTTAC CTCCC AAAAT GTAACCACTG
GGAGAGAGAC CTGCTCCGGC CGTTGGAATG GAGGGTTTTA CATTGGTGAC

29951 TGAGCCCACC TCTCAAAAAA ACCAAGTCAA ACATAAACCT GGAAATATCT
ACTCGGGTGG AGAGTTTTTT TGGTTCAGTT TGTATTTGGA CCTTTATAGA

30001 GCACCCCTCA CAGTTACCTC AGAAGCCCTA ACTGTGGCTG CCGCCGCACC
CGTGGGGAGT GTCAATGGAG TCTTCGGGAT TGACACCGAC GCGGCGTG

30051 TCTAATGGTC GCGGGCAACA CACTCACCAT GCAATCACAG GCCCCGCTAA
AGATTACCAG CGCCCGTTGT GTGAGTGGTA CGTTAGTGTC CGGGGCGATT

30101 CCGTGCACGA CTCCAAACTT AGCATTGCCA CCCAAGGACC CCTCACAGTG
GGCACGTGCT GAGGTTTGAA TCGTAACGGT GGGTTCCTGG GGAGTGTAC

30151 TCAGAAGGAA AGCTAGCCCT GCAAACATCA GGCCCCCTCA CCACCACCGA
AGTCTTCCTT TCGATCGGA CGTTTGTAGT CCGGGGGAGT GGTGGTGGCT

30201 TAGCAGTACC CTTACTATCA CTGCCTCACC CCCTCTAACT ACTGCCACTG
ATCGTCATGG GAATGATAGT GACGGAGTGG GGGAGATTGA TGACGGTGAC

30251 GTAGCTTGGG CATTGACTTG AAAGAGCCCA TTTATACACA AAATGGAAAA
CATCGAACCC GTAACGAAC TTTCTCGGGT AAATATGTGT TTTACCTTTT

Figure 27 AF

30351 TTTGACCGTA GCAACTGGTC CAGGTGTGAC TATTAATAAT ACTTCCTTGC
AAACTGGCAT CGTTGACCAG GTCCACACTG ATAATTATTA TGAAGGAACG

30401 AAACATAAGT TACTGGAGCC TTGGGTTTTG ATTCACAAGG CAATATGCAA
TTTGATTTC AATGACCTCGG AACCCAAAAC TAAGTGTTC GTTATACGTT

30451 CTTAATGTAG CAGGAGGACT AAGGATTGAT TCTCAAAACA GACGCCTTAT
GAATTACATC GTCCTCCTGA TTCCTAACTA AGAGTTTTGT CTGCGGAATA

30501 ACTTGATGTT AGTTATCCGT TTGATGCTCA AAACCAACTA AATCTAAGAC
TGAACATCAA TCAATAGGCA AACTACGAGT TTTGGTTGAT TTAGATTCTG

30551 TAGGACAGGG CCCTCTTTTT ATAACTCAG CCCACAACCT GGATATTAAAC
ATCCTGTCCC GGGAGAAAAA TATTTGAGTC GGGTGTGAA CCTATAATTG

30601 TACAACAAAG GCCTTTACTT GTTTACAGCT TCAAACAATT CCAAAAAGCT
ATGTTGTTTC CGGAAATGAA CAAATGTCGA AGTTTGTAA GGTTTTTCGA

30651 TGAGGTAAAC CTAAGCACTG CCAAGGGGTT GATGTTTGAC GCTACAGCCA
ACTCCAATTG GATTCGTGAC GGTTCCTCAA CTACAACTG CGATGTCGGT

30701 TAGCCATTAA TGCAGGAGAT GGGCTTGAAT TTGGTTCACC TAATGCACCA
ATCGGTAATT ACGTCCTCTA CCCGAACCTA AACCAAGTGG ATTACGTGGT

30751 AACACAAATC CCCTCAAAAC AAAAATTGGC CATGGCCTAG AATTTGATTC
TTGTGTTTAG GGGAGTTTTG TTTTAAACCG GTACCGGATC TTAAACTAAG

30801 AAACAAGGCT ATGGTTCCTA AACTAGGAAC TGGCCTTAGT TTTGACAGCA
TTTGTTCCTA TACCAAGGAT TTGATCCTTG ACCGGAATCA AAACGTGCTG

30851 CAGGTGCCAT TACAGTAGGA AACAAAAATA ATGATAAGCT AACTTTGTGG
GTCCACGGTA ATGTCATCCT TTGTTTTTAT TACTATTCTA TTGAAACACC

30901 ACCACACCAG CTCCATCTCC TAACTGTAGA CTAAATGCAG AGAAAGATGC
TGGTGTGGTC GAGGTAGAGG ATTGACATCT GATTTACGTC TCTTCTACG

30951 TAAACTCACT TTGGTCTTAA CAAAATGTGG CAGTCAAATA CTTGCTACAG
ATTTGAGTGA AACCAGAATT GTTTTACACC GTCAGTTTAT GAACGATGTC

31001 TTTCACTTTT GGCTGTTAAA GGCAGTTTGG CTCCAATATC TGGAACAGTT
AAAGTCAAAA CCGACAATTT CCGTCAAACC GAGGTTATAG ACCTTGTCAT

31051 CAAAGTGCTC ATCTTATTAT AAGATTTGAC GAAAATGGAG TGCTACTAAA
GTTTCACGAG TAGAATAATA TTCTAACTG CTTTTACCTC ACGATGATTT

31101 CAATTCCCTC CTGGACCCAG AATATTGGAA CTTTAGAAAT GGAGATCTTA
GTTAAGGAAG GACCTGGGTC TTATAACCTT GAAATCTTTA CCTCTAGAAT

31151 CTGAAGGCAC AGCCTATACA AACGCTGTTG GATTTATGCC TAACCTATCA
GACTTCCGTG TCGGATATGT TTGCGACAAC CTAAATACGG ATTGGATAGT

31201 GCTTATCCAA AATCTCACGG TAAACTGCC AAAAGTAACA TTGTCAGTCA
CGAATAGGTT TTAGAGTGCC ATTTTGACGG TTTTCATTGT AACAGTCAGT

Figure 27 AG

31251 AGTTTACT... AACGGAGACA AACTTAAACC TGTAACAC... ACCATTACAC
TCAAATGAAT TTGCCTCTGT TTTGATTTGG ACATTGTGAT TGGTAATGTG

31301 TAAACGGTAC ACAGGAAACA GGAGACACAA CTCCAAGTGC ATACTCTATG
ATTTGCCATG TGTCCTTTGT CCTCTGTGTT GAGGTTTCACG TATGAGATAC

31351 TCATTTTCAT GGGACTGGTC TGGCCACAAC TACATTAATG AAATATTTGC
AGTAAAAGTA CCCTGACCAG ACCGGTGTG ATGTAATTAC TTTATAAACG

31401 CACATCCTCT TACACTTTTT CATAATTGC CCAAGAATAA AGAATCGTTT
GTGTAGGAGA ATGTGAAAAA GTATGTAACG GGTTCCTTATT TCTTAGCAAA

31451 GTGTTATGTT TCAACGTGTT TATTTTTCAA TTGCAGAAAA TTTCAAGTCA
CACAATACAA AGTTGCACAA ATAAAAAGTT AACGTCTTTT AAAGTTCAGT

31501 TTTTTCATTC AGTAGTATAG CCCCACCACC ACATAGCTTA TACAGATCAC
AAAAAGTAAG TCATCATATC GGGGTGGTGG TGTATCGAAT ATGTCTAGTG

31551 CGTACCCTAA TCAAACTCAC AGAACCCCTAG TATTCAACCT GCCACCTCCC
GCATGGAATT AGTTTGAGTG TCTTGGGATC ATAAGTTGGA CGGTGGAGGG

31601 TCCCAACACA CAGAGTACAC AGTCCTTTCT CCCC GGCTGG CCTTAAAAAG
AGGGTTGTGT GTCTCATGTG TCAGGAAAGA GGGGCCGACC GGAATTTTTC

31651 CATCATATCA TGGGTAACAG ACATATTCTT AGGTGTTATA TTCCACACGG
GTAGTATAGT ACCCATTTGTC TGTATAAGAA TCCACAATAT AAGGTGTGCC

31701 TTTCTGTGCG AGCCAAACGC TCATCAGTGA TATTAATAAA CTCCCCGGGC
AAAGGACAGC TCGGTTTGCG AGTAGTCACT ATAATTATTT GAGGGGCCCG

31751 AGCTCACTTA AGTTCATGTC GCTGTCCAGC TGCTGAGCCA CAGGCTGCTG
TCGAGTGAAT TCAAGTACAG CGACAGGTCG ACGACTCGGT GTCCGACGAC

31801 TCCAACTTGC GGTGCTTAA CGGGCGGCGA AGGAGAAGTC CACGCCTACA
AGGTTGAACG CCAACGAATT GCCCGCCGCT TCCTCTTCAG GTGCGGATGT

31851 TGGGGGTAGA GTCATAATCG TGCATCAGGA TAGGGCGGTG GTGCTGCAGC
ACCCCCATCT CAGTATTAGC ACGTAGTCCT ATCCCGCCAC CACGACGTCTG

31901 AGCGCGCGAA TAACTGCTG CCGCCGCCGC TCCGTCCTGC AGGAATACAA
TCGCGCGCTT ATTTGACGAC GCGCGCGGCG AGGCAGGACG TCCTTATGTT

31951 CATGGCAGTG GTCTCCTCAG CGATGATTCG CACCGCCCGC AGCATAAGGC
GTACCGTCAC CAGAGGAGTC GCTACTAAGC GTGGCGGGCG TCGTATTCCG

32001 GCCTTGTCCT CCGGGCACAG CAGCGCACCC TGATCTCACT TAAATCAGCA
CGGAACAGGA GGCCCGTGTC GTCGCGTGGG ACTAGAGTGA ATTTAGTCGT

32051 CAGTAACTGC AGCACAGCAC CACAATATTG TTCAAAATCC CACAGTGCAA
GTCATTGACG TCGTGTCTGT GTGTTATAAC AAGTTTATAGG GTGTCACGTT

32101 GCGCTGTAT CCAAAGCTCA TGGCGGGGAC CACAGAACCC ACGTGCCAT
CCGCGACATA GGTTCGAGT ACCGCCCCTG GTGTCTTGGG TGCACCGGTA

32151 CATACCACAA GCGCAGGTAG ATTAAGTGGC GACCCCTCAT AAACACGCTG
GTATGGTGTT CGCGTCCATC TAATTCACCG CTGGGGAGTA TTTGTGCGAC

Figure 27AH

32251 CCATATAAAC CTCTGATTAA ACATGGCGCC ATCCACCACC ATCCTAAACC
 GGTATATTTG GAGACTAATT TGTACCGCGG TAGGTGGTGG TAGGATTTGG
 32301 AGCTGGCCAA AACCTGCCCC CCGGCTATAC ACTGCAGGGA ACCGGGACTG
 TCGACCGGTT TTGGACGGGC GGCCGATATG TGACGTCCCT TGGCCCTGAC
 32351 GAACAATGAC AGTGGAGAGC CCAGGACTCG TAACCATGGA TCATCATGCT
 CTTGTTACTG TCACCTCTCG GGTCTGAGC ATTGGTACCT AGTAGTACGA
 32401 CGTCATGATA TCAATGTTGG CACAACACAG GCACACGTGC ATACACTTCC
 GCAGTACTAT AGTTACAACC GTGTTGTGTC CGTGTGCACG TATGTGAAGG
 32451 TCAGGATTAC AAGCTCCTCC CGCGTTAGAA CCATATCCCA GGGAAACAACC
 AGTCCTAATG TTCGAGGAGG GCGCAATCTT GGTATAGGGT CCCTTGTTGG
 32501 CATTCCTGAA TCAGCGTAAA TCCCACACTG CAGGGAAGAC CTCGCACGTA
 GTAAGGACTT AGTCGCATTT AGGGTGTGAC GTCCCTTCTG GAGCGTGCAT
 32551 ACTCACGTTG TGCATTGTCA AAGTGTTACA TTCGGGCAGC AGCGGATGAT
 TGAGTGCAAC ACGTAACAGT TTCACAATGT AAGCCCCTCG TCGCCTACTA
 32601 CCTCCAGTAT GGTAGCGCGG GTTTCTGTCT CAAAAGGAGG TAGACGATCC
 GGAGGTCATA CCATCGCGCC CAAAGACAGA GTTTTCCTCC ATCTGCTAGG
 32651 CTA CTGTACG GAGTGCGCCG AGACAACCGA GATCGTGTTG GTCGTAGTGT
 GATGACATGC CTCACGCGGC TCTGTTGGCT CTAGCACAAC CAGCATCACA
 32701 CATGCCAAAT GGAACGCCCG ACGTAGTCAT ATTTCTTGAA GCAAAACCAG
 GTACGGTTTA CCTTGCGGCC TGCATCAGTA TAAAGGACTT CGTTTTGGTC
 32751 GTGCGGGCGT GACAAACAGA TCTGCGTCTC CGGTCTCGCC GCTTAGATCG
 CACGCCCGCA CTGTTTGTCT AGACGCAGAG GCCAGAGCGG CGAATCTAGC
 32801 CTCTGTGTAG TAGTTGTAGT ATATCCACTC TCTCAAAGCA TCCAGGCGCC
 GAGACACATC ATCAACATCA TATAGGTGAG AGAGTTTCGT AGGTCCGCGG
 32851 CCCTGGCTTC GGGTTCTATG TAAACTCCTT CATGCGCCGC TGCCCTGATA
 GGGACCGAAG CCAAGATAC ATTTGAGGAA GTACGCGGCG ACGGGACTAT
 32901 ACATCCACCA CCGCAGAATA AGCCACACCC AGCCAACCTA CACATTCTGT
 TGTAGGTGGT GCGGTCTTAT TCGGTGTGGG TCGGTGGAT GTGTAAGCAA
 32951 CTGCGAGTCA CACACGGGAG GAGCGGGAAG AGCTGGAAGA ACCATGTTTT
 GACGCTCAGT GTGTGCCCTC CTCGCCCTTC TCGACCTTCT TGGTACAAAA
 33001 TTTTTTTTATT CAAAAGATT ATCCAAAACC TCAAATGAA GATCTATTAA
 AAAAAATAA GGTTTTCTAA TAGGTTTTGG AGTTTTACTT CTAGATAATT
 33051 GTGAACGCGC TCCCCTCCGG TGGCGTGGTC AACTCTACA GCCAAAGAAC
 CACTTGCGCG AGGGGAGGCC ACCGCACCAG TTTGAGATGT CGGTTTCTTG
 33101 AGATAATGGC ATTTGTAAGA TGTTGCACAA TGGCTTCCAA AAGGCAAACG
 TCTATTACCG TAAACATTCT ACAACGTGTT ACCGAAGGTT TTCCGTTTGC

Figure 27 AI

33201 CTCTATAAAC ATTCCAGCAC CTTCAACCAT GCCCAAATAA TTCTCATCTC
GAGATATTTG TAAGGTCGTG GAAGTTGGTA CGGGTTTATT AAGAGTAGAG

33251 GCCACCTTCT CAATATATCT CTAAGCAAAT CCCGAATATT AAGTCGGGCC
CGGTGGAAGA GTTATATAGA GATTCGTTTA GGGCTTATAA TTCAGGCCGG

33301 ATTGTAAGAAA TCTGCTCCAG AGCGCCCTCC ACCTTCAGCC TCAAGCAGCG
TAACATTTTT AGACGAGGTC TCGCGGGAGG TGAAGTCGG AGTTCGTCGC

33351 AATCATGATT GCAAAAATTC AGGTTCTCTCA CAGACCTGTA TAAGATTCAA
TGTACTATAA CGTTTTTAAG TCCAAGGAGT GTCTGGACAT ATTCTAAGTT

33401 AAGCGGAACA TTAACAAAAA TACCGCGATC CCGTAGGTCC CTTGCGAGGG
TTCGCCTTGT AATTGTTTTT ATGGCGCTAG GGCATCCAGG GAAGCGTCCC

33451 CCAGCTGAAC ATAATCGTGC AGGTCTGCAC GGACCAGCGC GGCCACTTCC
GGTCGACTTG TATTAGCACG TCCAGACGTG CCTGGTCGCG CCGGTGAAGG

33501 CCGCCAGGAA CCATGACAAA AGAACCACCA CTGATTATGA CACGCATACT
GGCGGTCTTT GGTACTGTTT TCTTGGGTGT GACTAATACT GTGCGTATGA

33551 CGGAGCTATG CTAACCAGCG TAGCCCCGAT GTAAGCTTGT TGCATGGGCG
GCCTCGATAC GATTGGTCGC ATCGGGGCTA CATTCAACA ACGTACCCGC

33601 GCGATATAAA ATGCAAGGTG CTGCTCAAAA AATCAGGCAA AGCCTCGCGC
CGCTATATTT TACGTTCAC GACGAGTTTT TTAGTCCGTT TCGGAGCGCG

33651 AAAAAAGAAA GCACATCGTA GTCATGCTCA TGCAGATAAA GGCAGGTAAG
TTTTTCTTT CGTGTAGCAT CAGTACGAGT ACGTCTATTT CCGTCCATTC

33701 CTCCGGAACC ACCACAGAAA AAGACACCAT TTTTCTCTCA AACATGTCTG
GAGGCCTTGG TGGTGTCTTT TTCTGTGGTA AAAAGAGAGT TTGTACAGAC

33751 CGGGTTTCTG CATAAACACA AAATAAAATA ACAAAAAAAC ATTTAAACAT
GCCCCAAGAC GTATTTGTGT TTTATTTTAT TGTTTTTTTG TAAATTTGTA

33801 TAGAAGCCTG TCTTACAACA GGAAAAACAA CCCTTATAAG CATAAGACGG
ATCTTCGGAC AGAATGTTGT CCTTTTTGTT GGAATATTC GTATTCTGCC

33851 ACTACGGCCA TGCCGGCGTG ACCGTAAAAA AACTGGTCAC CGTGATTAAA
TGATGCCGGT ACGGCCGCAC TGGCATTITT TTGACCAGTG GCACTAATTT

33901 AAGCACCACC GACAGCTCCT CGGTCATGTC CGGAGTCATA ATGTAAGACT
TTCGTGGTGG CTGTGAGGA GCCAGTACAG GCCTCAGTAT TACATTCTGA

33951 CGGTAAACAC ATCAGGTTGA TTCACATCGG TCAGTGCTAA AAAGCGACCG
GCCATTTGTG TAGTCCAAC AAGTGTAGCC AGTCACGATT TTTCGCTGGC

34001 AAATAGCCCG GGGGAATACA TACCCGAGG CGTAGAGACA ACATTACAGC
TTTATCGGGC CCCCTTATGT ATGGGCGTCC GCATCTCTGT TGTAAATGTCG

34051 CCCCATAGGA GGTATAACAA AATTAATAGG AGAGAAAAAC ACATAAACAC
GGGGTATCCT CCATATTGTT TTAATTATCC TCTCTTTTGT TGTATTTGTG

Figure 27A5

34151	ACATACAGCG	CTTCCACAGC	GGCAGCCATA	ACAGTCAGCC	TTACCAGTAA
	TGTATGTCGC	GAAGGTGTCG	CCGTCGGTAT	TGTCAGTCGG	AATGGTCATT
34201	AAAAGAAAAC	CTATTAAAAA	AACACCACTC	GACACGGCAC	CAGCTCAATC
	TTTTCTTTTG	GATAATTTTT	TTGTGGTGAG	CTGTGCCGTG	GTCGAGTTAG
34251	AGTCACAGTG	TAAAAAAGGG	CCAAGTGCAG	AGCGAGTATA	TATAGGACTA
	TCAGTGTCAC	ATTTTTTCCC	GGTTCACGTC	TCGCTCATAT	ATATCCTGAT
34301	AAAAATGACG	TAACGGTTAA	AGTCCACAAA	AAACACCCAG	AAAACCGCAC
	TTTTTACTGC	ATTGCCAATT	TCAGGTGTTT	TTTGTGGGTC	TTTTTGGCGTG
34351	GCGAACCTAC	GCCCAGAAAC	GAAAGCCAAA	AAACCCACAA	CTTCCTCAAA
	CGCTTGATG	CGGGTCTTTG	CTTTCGGTTT	TTTGGGTGTT	GAAGGAGTTT
34401	TCGTCACTTC	CGTTTTCCCA	CGTTACGTCA	CTTCCCATT	TAAGAAAAC
	AGCAGTGAAG	GCAAAAGGGT	GCAATGCAGT	GAAGGGTAAA	ATTCTTTTGA
34451	ACAATTCCCA	ACACATACAA	GTTACTCCGC	CCTAAAACCT	ACGTCACCCG
	TGTTAAGGGT	TGTGTATGTT	CAATGAGGCG	GGATTTTGGA	TGCAGTGGGC
34501	CCCCGTTCCT	ACGCCCCGCG	CCACGTCACA	AACTCCACCC	CCTCATTATC
	GGGGCAAGGG	TGCGGGGCGC	GGTGCAAGGT	TTGAGGTGGG	GGAGTAATAG
				PacI	

34551	ATATTGGCTT	CAATCCAAAA	TAAGGTATAT	TATTGATGAT	GTTAATTAAG
	TATAACCGAA	GTTAGGTTTT	ATTCCATATA	ATAACTACTA	CAATTAATTC
34601	AATTCGGATC	TGCGACGCGA	GGCTGGATGG	CCTTCCCCAT	TATGATTCTT
	TTAAGCCTAG	ACGCTGCGCT	CCGACCTACC	GGAAGGGGTA	ATACTAAGAA
34651	CTCGCTTCCG	GCGGCATCGG	GATGCCCCGCG	TTGCAGGCCA	TGCTGTCCAG
	GAGCGAAGGC	CGCCGTAGCC	CTACGGGCGC	AACGTCCGGT	ACGACAGGTC
34701	GCAGGTAGAT	GACGACCATC	AGGGACAGCT	TCAAGGCCAG	CAAAAGGCCA
	CGTCCATCTA	CTGCTGGTAG	TCCCTGTCTGA	AGTTCCGGTC	GTTTTCCGGT
34751	GGAACCGTAA	AAAGGCCGCG	TTGCTGGCGT	TTTTCCATAG	GCTCCGCCCC
	CCTTGGCATT	TTTCCGGCGC	AACGACCGCA	AAAAGGTATC	CGAGGCGGGG
34801	CCTGACGAGC	ATCACAAAAA	TCGACGCTCA	AGTCAGAGGT	GGCGAAACCC
	GGACTGCTCG	TAGTGTTTTT	AGCTGCGAGT	TCAGTCTCCA	CCGCTTTGGG
34851	GACAGGACTA	TAAAGATACC	AGGCGTTTCC	CCCTGGAAGC	TCCCTCGTGC
	CTGTCCTGAT	ATTTCTATGG	TCCGCAAAGG	GGGACCTTCG	AGGGAGCACG
34901	GCTCTCCTGT	TCCGACCCTG	CCGCTTACCG	GATACCTGTC	CGCCTTTCTC
	CGAGAGGACA	AGGCTGGGAC	GGCGAATGGC	CTATGGACAG	GCGGAAAGAG
34951	CCTTCGGGAA	GCGTGGCGCT	TTCTCATAGC	TCACGCTGTA	GGTATCTCAG
	GGAAGCCCTT	CGCACC CGCA	AAGAGTATCG	AGTGCGACAT	CCATAGAGTC
35001	TTCCGGTGTAG	GTCGTTTCGCT	CCAAGCTGGG	CTGTGTGCAC	GAACCCCCCG
	AAGCCACATC	CAGCAAGCGA	GGTTCGACCC	GACACACGTG	CTTGGGGGGC

Figure 27 AK

```

AAGTCGGGCT GCGGACGCGG AATAGGCCAT TGATAGCAGA ACTCAGGTTG
35101 CCGGTAAGAC ACGACTTATC GCCACTGGCA GCAGCCACTG GTAACAGGAT
      GGCCATTCTG TGCTGAATAG CGGTGACCGT CGTCGGTGAC CATTGTCCTA
35151 TAGCAGAGCG AGGTATGTAG GCGGTGCTAC AGAGTTCTTG AAGTGGTGGC
      ATCGTCTCGC TCCATACATC CGCCACGATG TCTCAAGAAC TTCACCACCG
35201 CTAACTACGG CTACACTAGA AGGACAGTAT TTGGTATCTG CGCTCTGCTG
      GATTGATGCC GATGTGATCT TCCTGTCATA AACCATAGAC GCGAGACGAC
35251 AAGCCAGTTA CCTTCGAAA AAGAGTTGGT AGCTCTTGAT CCGGCAAACA
      TTCGGTCAAT GGAAGCCTTT TTCTCAACCA TCGAGAACTA GGCCGTTTGT
35301 AACCACCGCT GGTAGCGGTG GTTTTTTTGT TTGCAAGCAG CAGATTACGC
      TTGGTGCGA CCATCGCCAC CAAAAAACA AACGTTTCGT GTCTAATGCG
35351 GCAGAAAAAA AGGATCTCAA GAAGATCCTT TGATCTTTTC TACGGGGTCT
      CGTCTTTTTT TCCTAGAGTT CTCTAGGAA ACTAGAAAAG ATGCCCCAGA
35401 GACGCTCAGT GGAACGAAAA CTCACGTAA GGGATTTTGG TCATGAGATT
      CTGCGAGTCA CCTTGCTTTT GAGTGCAATT CCCTAAAACC AGTACTCTAA
35451 ATCAAAAAGG ATCTTCACCT AGATCCTTTT AAATCAATCT AAAGTATATA
      TAGTTTTTCC TAGAAGTGGA TCTAGGAAAA TTTAGTTAGA TTTCATATAT
35501 TGAGTAAACT TGGTCTGACA GTTACCAATG CTTAATCAGT GAGGCACCTA
      ACTCATTTGA ACCAGACTGT CAATGGTTAC GAATTAGTCA CTCCGTGGAT
35551 TCTCAGCGAT CTGTCTATTT CGTTCATCCA TAGTTGCCTG ACTCCCCGTC
      AGAGTCGCTA GACAGATAAA GCAAGTAGGT ATCAACGGAC TGAGGGGCAG
35601 GTGTAGATAA CTACGATACG GGAGGGCTTA CCATCTGGCC CCAGTGCTGC
      CACATCTATT GATGCTATGC CCTCCGAAT GGTAGACCGG GGTCACGACG
35651 AATGATACCG CGAGACCCAC GCTCACC GGC TCCAGATTTA TCAGCAATAA
      TTACTATGGC GCTCTGGGTG CGAGTGGCCG AGGTCTAAAT AGTCGTTATT
35701 ACCAGCCAGC CGGAAGGGCC GAGCGCAGAA GTGGTCCTGC AACTTTATCC
      TGGTCGGTCG GCCTTCCCGG CTCGCGTCTT CACCAGGACG TTGAAATAGG
35751 GCCTCCATCC AGTCTATTAA TTGTTGCCGG GAAGCTAGAG TAAGTAGTTC
      CGGAGGTAGG TCAGATAATT AACAACGGCC CTTGATCTC ATTCATCAAG
35801 GCCAGTTAAT AGTTTGCGCA AC GTTGTTGC CATTGCTACA GGCATCGTGG
      CGGTCAATTA TCAAACGCGT TGCAACAACG GTAACGATGT CCGTAGCACC
35851 TGTCACGCTC GTCGTTTGGT ATGGCTTCAT TCAGCTCCGG TTCCCAACGA
      ACAGTGCGAG CAGCAAACCA TACCGAAGTA AGTCGAGGCC AAGGGTTGCT
35901 TCAAGGCGAG TTACATGATC CCCCATGTTG TGCAAAAAAG CGGTTAGCTC
      AGTTCCGCTC AATGTACTAG GGGGTACAAC ACGTTTTTTC GCCAATCGAG
35951 CTTCCGGTCCT CCGATCGTTG TCAGAAGTAA GTTGGCCGCA GTGTTATCAC
      GAAGCCAGGA GGCTAGCAAC AGTCTTCATT CAACCGGCGT CACAATAGTG

```

Figure 2 TAL

36051 AGATGCTTTT CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATA
TCTACGAAAA GACACTGACC ACTCATGAGT TGGTTCAGTA AGACTCTTAT

36101 GTGTATGCGG CGACCGAGTT GCTCTTGCCC GCGGTCAACA CGGGATAATA
CACATACGCC GCTGGCTCAA CGAGAACGGG CCGCAGTTGT GCCCTATTAT

36151 CCGCGCCACA TAGCAGAACT TTAAAAGTGC TCATCATTGG AAAACGTTCT
GGCGCGGTGT ATCGTCTTGA AATTTTACAG AGTAGTAACC TTTTGCAAGA

36201 TCGGGGCGAA AACTCTCAAG GATCTTACCG CTGTTGAGAT CCAGTTCGAT
AGCCCCGCTT TTGAGAGTTC CTAGAATGGC GACAACCTTA GGTCAAGCTA

36251 GTAACCCACT CGTGACCCCA ACTGATCTTC AGCATCTTTT ACTTTCACCA
CATTGGGTGA GCACGTGGGT TGACTAGAAG TCGTAGAAAA TGAAAGTGGT

36301 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA
CGCAAAGACC CACTCGTTTT TGTCCTTCCG TTTTACGGCG TTTTTTCCCT

36351 ATAAGGGCGA CACGGAAATG TTGAATACTC ATACTCTTCC TTTTCAATA
TATTCCCCTG GTGCCTTTAC AACTTATGAG TATGAGAAGG AAAAAGTTAT

36401 TTATTGAAGC ATTTATCAGG GTTATTGTCT CATGAGCGGA TACATATTTG
AATAACTTCG TAAATAGTCC CAATAACAGA GTACTCGCCT ATGTATAAAC

36451 AATGTATTTA GAAAAATAAA CAAATAGGGG TTCCGCGCAC ATTTCCCCGA
TTACATAAAT CTTTTTATTT GTTTATCCCC AAGGCGCGTG TAAAGGGGCT

36501 AAAGTGCCAC CTGACGTCTA AGAAACCATT ATTATCATGA CATTAAACCTA
TTTCACGGTG GACTGCAGAT TCTTTGGTAA TAATAGTACT GTAATTGGAT

36551 TAAAAATAGG CGTATCACGA GGCCCTTTTCG TCTTCAAGAA TTGGATCCGA
ATTTTTATCC GCATAGTGCT CCGGGAAAGC AGAAGTTCTT AACCTAGGCT

PacI

36601 ATTCTTAATT TCTTAATTAA (SEQ ID NO:34)
TAAGAATTAA AGAATTAATT (SEQ ID NO:35)

Figure 27AM

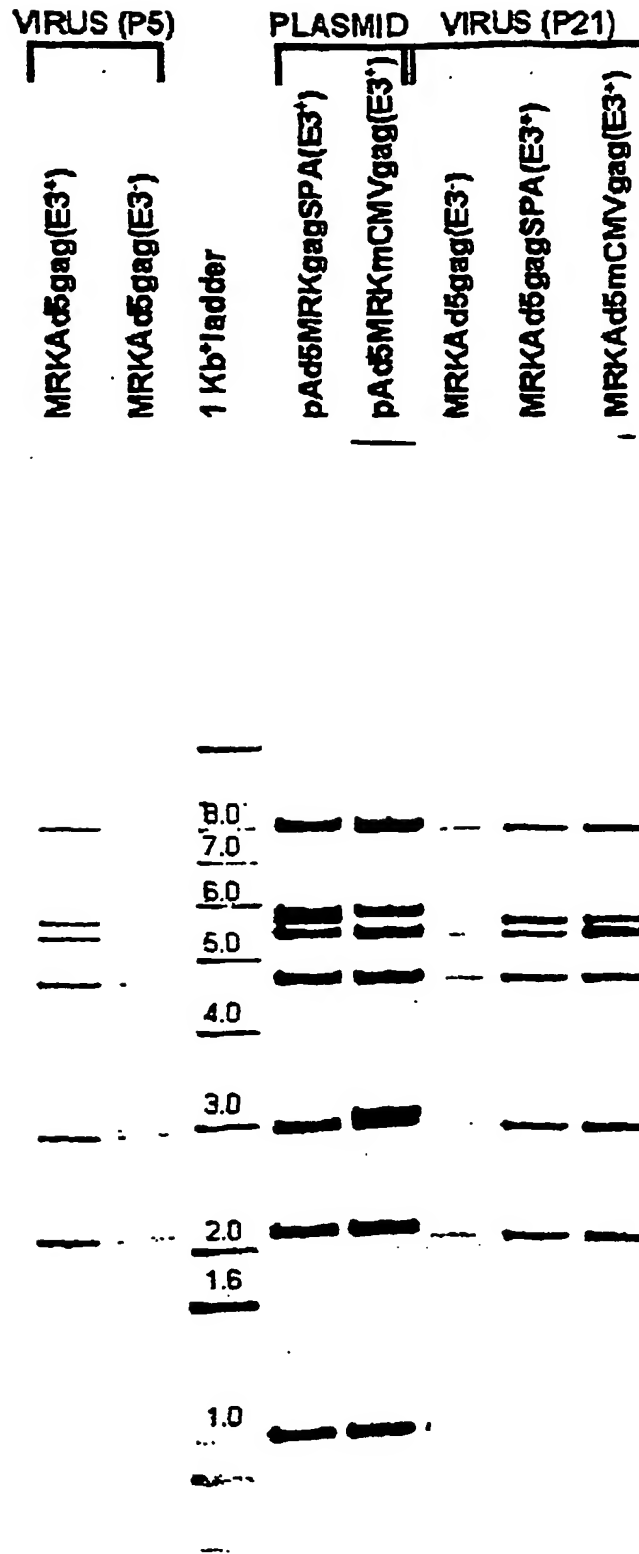


FIGURE 28

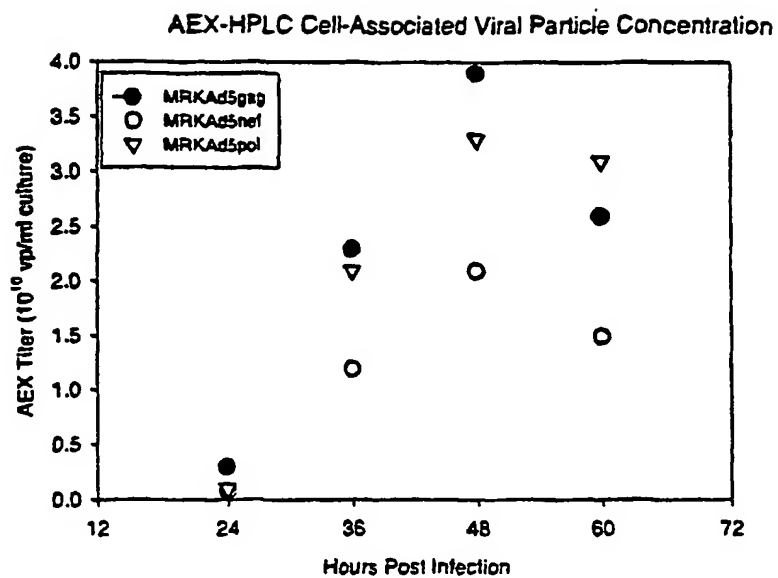


FIGURE 29A

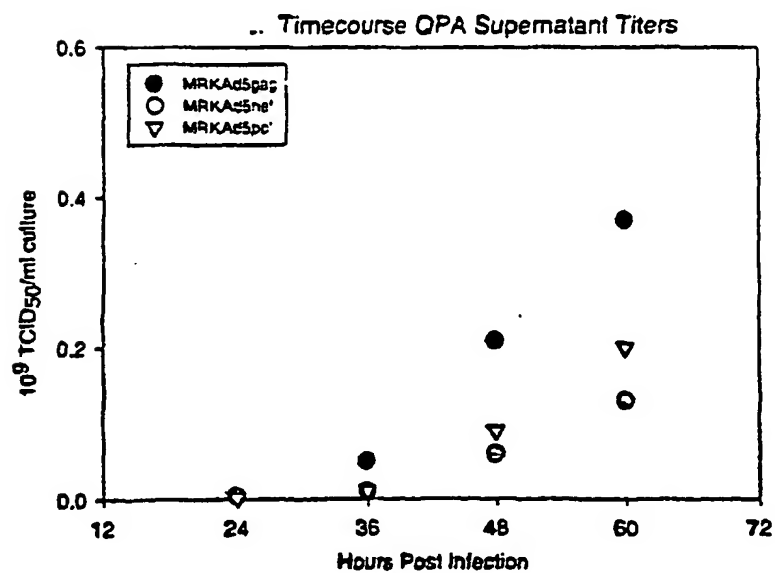


FIGURE 29B

atg gat gca atg aag aga ggg ctc tgc tgt gtg ctg ctg ctg tgt gga Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly 1 5 10 15	48
gca gtc ttc gtt tgc ccc agc gag atc tcc att gtg tgg gcc tcc agg Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ile Val Trp Ala Ser Arg 20 25 30	96
gag ctg gag agg ttt gct gtg aac cct ggc ctg ctg gag acc tct gag Glu Leu Glu Arg Phe Ala Val Asn Pro Gly Leu Leu Glu Thr Ser Glu 35 40 45	144
ggg tgc agg cag atc ctg ggc cag ctc cag ccc tcc ctg caa aca ggc Gly Cys Arg Gln Ile Leu Gly Gln Leu Gln Pro Ser Leu Gln Thr Gly 50 55 60	192
tct gag gag ctg agg tcc ctg tac aac aca gtg gct acc ctg tac tgt Ser Glu Glu Leu Arg Ser Leu Tyr Asn Thr Val Ala Thr Leu Tyr Cys 65 70 75 80	240
gtg cac cag aag att gat gtg aag gac acc aag gag gcc ctg gag aag Val His Gln Lys Ile Asp Val Lys Asp Thr Lys Glu Ala Leu Glu Lys 85 90 95	288
att gag gag gag cag aac aag tcc aag aag aag gcc cag cag gct gct Ile Glu Glu Glu Gln Asn Lys Ser Lys Lys Lys Ala Gln Gln Ala Ala 100 105 110	336
gct ggc aca ggc aac tcc agc cag gtg tcc cag aac tac ccc att gtg Ala Gly Thr Gly Asn Ser Ser Gln Val Ser Gln Asn Tyr Pro Ile Val 115 120 125	384
cag aac ctc cag ggc cag atg gtg cac cag gcc atc tcc ccc cgg acc Gln Asn Leu Gln Gly Gln Met Val His Gln Ala Ile Ser Pro Arg Thr 130 135 140	432
ctg aat gcc tgg gtg aag gtg gtg gag gag aag gcc ttc tcc cct gag Leu Asn Ala Trp Val Lys Val Val Glu Glu Lys Ala Phe Ser Pro Glu 145 150 155 160	480
gtg atc ccc atg ttc tct gcc ctg tct gag ggt gcc acc ccc cag gac Val Ile Pro Met Phe Ser Ala Leu Ser Glu Gly Ala Thr Pro Gln Asp 165 170 175	528
ctg aac acc atg ctg aac aca gtg ggg ggc cat cag gct gcc atg cag Leu Asn Thr Met Leu Asn Thr Val Gly Gly His Gln Ala Ala Met Gln 180 185 190	576
atg ctg aag gag acc atc aat gag gag gct gct gag tgg gac agg ctg Met Leu Lys Glu Thr Ile Asn Glu Glu Ala Ala Glu Trp Asp Arg Leu 195 200 205	624
cat cct gtg cac gct ggc ccc att gcc ccc ggc cag atg agg gag ccc His Pro Val His Ala Gly Pro Ile Ala Pro Gly Gln Met Arg Glu Pro 210 215 220	672
agg ggc tct gac att gct ggc acc acc tcc acc ctc cag gag cag att Arg Gly Ser Asp Ile Ala Gly Thr Thr Ser Thr Leu Gln Glu Gln Ile 225 230 235 240	720
ggc tgg atg acc aac aac ccc ccc atc cct gtg ggg gaa atc tac aag Gly Trp Met Thr Asn Asn Pro Pro Ile Pro Val Gly Glu Ile Tyr Lys 245 250 255	768

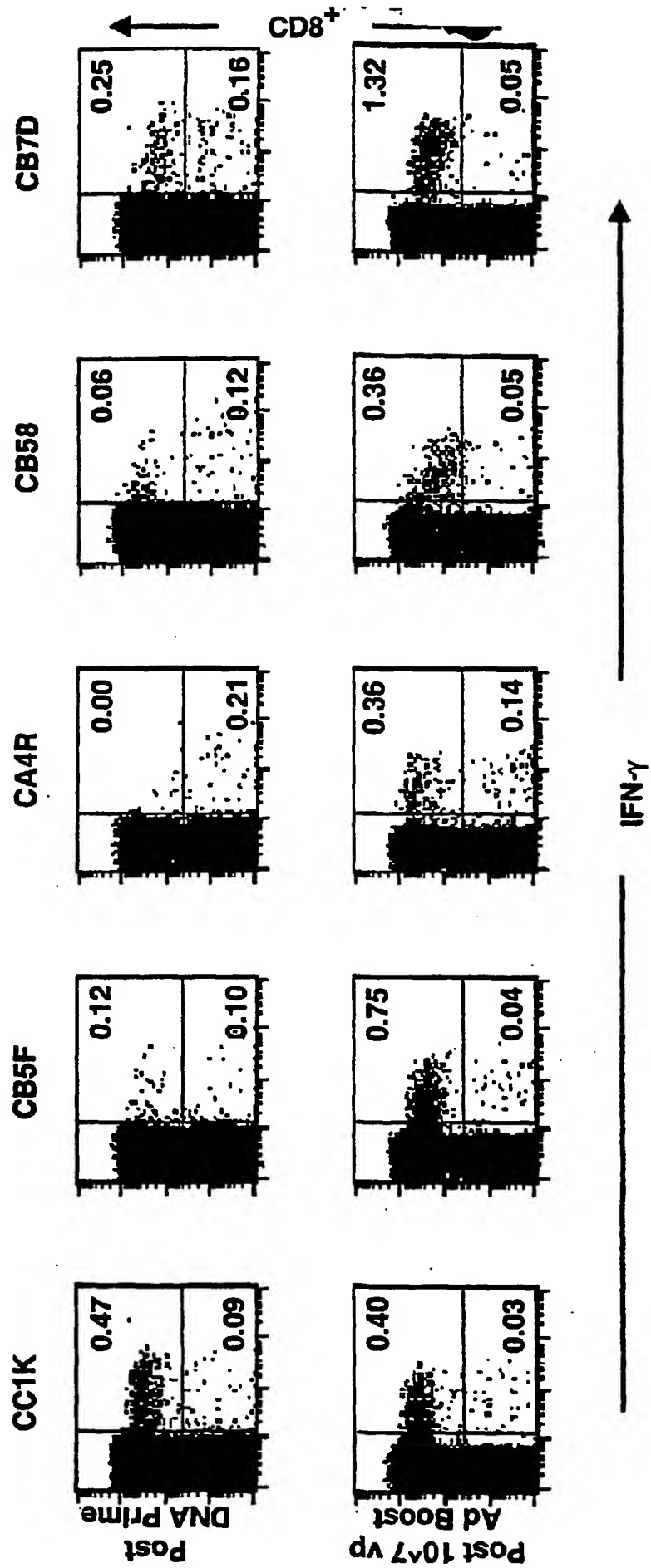
Figure 30A

agg tgg atc atc ctg ggc ctg aac aag att gtg agg atg tac tcc ccc	816
Arg Trp Ile Ile Leu Gly Leu Asn Lys Ile Val Arg Met Tyr Ser Pro	
260 265 270	
acc tcc atc ctg gac atc agg cag ggc ccc aag gag ccc ttc agg gac	864
Thr Ser Ile Leu Asp Ile Arg Gln Gly Pro Lys Glu Pro Phe Arg Asp	
275 280 285	
tat gtg gac agg ttc tac aag acc ctg agg gct gag cag gcc tcc cag	912
Tyr Val Asp Arg Phe Tyr Lys Thr Leu Arg Ala Glu Gln Ala Ser Gln	
290 295 300	
gag gtg aag aac tgg atg aca gag acc ctg ctg gtg cag aat gcc aac	960
Glu Val Lys Asn Trp Met Thr Glu Thr Leu Leu Val Gln Asn Ala Asn	
305 310 315 320	
cct gac tgc aag acc atc ctg aag gcc ctg ggc cct gct gcc acc ctg	1008
Pro Asp Cys Lys Thr Ile Leu Lys Ala Leu Gly Pro Ala Ala Thr Leu	
325 330 335	
gag gag atg atg aca gcc tgc cag ggg gtg ggg ggc cct ggt cac aag	1056
Glu Glu Met Met Thr Ala Cys Gln Gly Val Gly Gly Pro Gly His Lys	
340 345 350	
gcc agg gtg ctg gct gag gcc atg tcc cag gtg acc aac tcc gcc acc	1104
Ala Arg Val Leu Ala Glu Ala Met Ser Gln Val Thr Asn Ser Ala Thr	
355 360 365	
atc atg atg cag agg ggc aac ttc agg aac cag agg aag aca gtg aag	1152
Ile Met Met Gln Arg Gly Asn Phe Arg Asn Gln Arg Lys Thr Val Lys	
370 375 380	
tgc ttc aac tgt ggc aag gtg ggc cac att gcc aag aac tgt agg gcc	1200
Cys Phe Asn Cys Gly Lys Val Gly His Ile Ala Lys Asn Cys Arg Ala	
385 390 395 400	
ccc agg aag aag ggc tgc tgg aag tgt ggc aag gag ggc cac cag atg	1248
Pro Arg Lys Lys Gly Cys Trp Lys Cys Gly Lys Glu Gly His Gln Met	
405 410 415	
aag gac tgc aat gag agg cag gcc aac ttc ctg ggc aaa atc tgg ccc	1296
Lys Asp Cys Asn Glu Arg Gln Ala Asn Phe Leu Gly Lys Ile Trp Pro	
420 425 430	
tcc cac aag ggc agg cct ggc aac ttc ctc cag tcc agg cct gag ccc	1344
Ser His Lys Gly Arg Pro Gly Asn Phe Leu Gln Ser Arg Pro Glu Pro	
435 440 445	
aca gcc cct ccc gag gag tcc ttc agg ttc ggg gag gag aag acc acc	1392
Thr Ala Pro Pro Glu Glu Ser Phe Arg Phe Gly Glu Glu Lys Thr Thr	
450 455 460	
ccc agc cag aag cag gag ccc att gac aag gag ctg tac ccc ctg gcc	1440
Pro Ser Gln Lys Gln Glu Pro Ile Asp Lys Glu Leu Tyr Pro Leu Ala	
465 470 475 480	
tcc ctg agg tcc ctg ttt ggc aac gac ccc tcc tcc cag taa (SID NO:36) 1482	
Ser Leu Arg Ser Leu Phe Gly Asn Asp Pro Ser Ser Gln * (SID NO:37)	
485 490	

Figure 30 B

Figure 31

IFN- γ Secretion against Gag 20-aa pool from CD3⁺ T cells of Monkey PBMCs



Comparison of Single-Modality Adenovirus Immunization with DNA+Adjuvant Prime/Adenovirus Boost

Immunizations

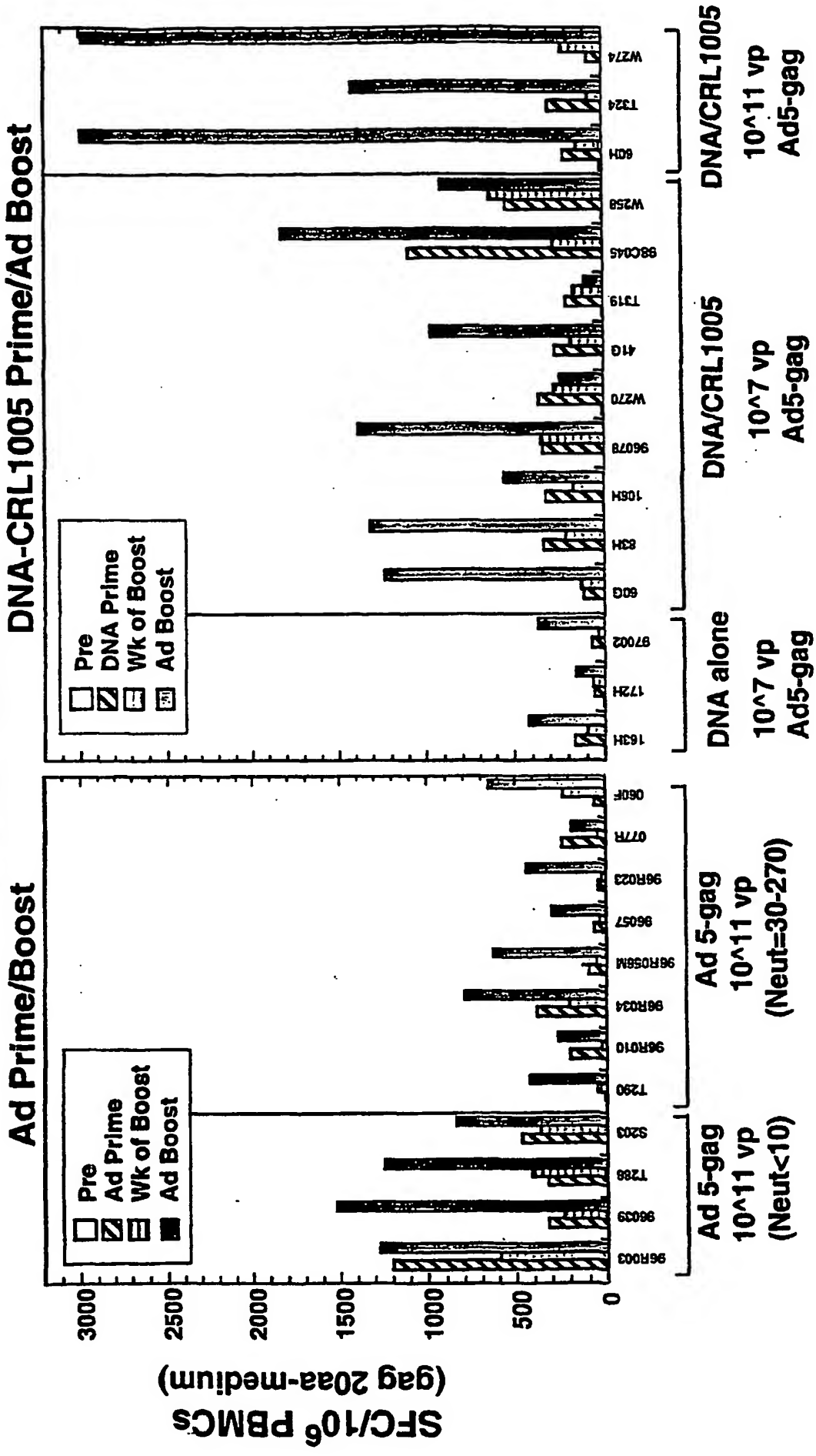


FIGURE 33A

ATGGGTGCTA GGGCTTCTGT GCTGTCTGGT GGTGAGCTGG ACAAGTGGGA GAAGATCAGG
CTGAGGCCTG GTGGCAAGAA GAAGTACAAG CTAAAGCACA TTGTGTGGGC CTCCAGGGAG
CTGGAGAGGT TTGCTGTGAA CCTTGGCCTG CTGGAGACCT CTGAGGGGTG CAGGCAGATC
CTGGGCCAGC TCCAGCCCTC CCTGCAAACA GGCTCTGAGG AGCTGAGGTC CCTGTACAAC
ACAGTGGCTA CCCTGTACTG TGTGCACCAG AAGATTGATG TGAAGGACAC CAAGGAGGCC
CTGGAGAAGA TTGAGGAGGA GCAGAACAAG TCCAAGAAGA AGGCCAGCA GGCTGCTGCT
GGCACAGGCA ACTCCAGCCA GGTGTCCCAG AACTACCCCA TTGTGCAGAA CCTCCAGGGC
CAGATGGTGC ACCAGGCCAT CTCCCCCGG ACCCTGAATG CCTGGGTGAA GGTGGTGGAG
GAGAAGGCCT TCTCCCCCTGA GGTGATCCCC ATGTTCTCTG CCCTGTCTGA GGGTGCCACC
CCCCAGGACC TGAACACCAT GCTGAACACA GTGGGGGGCC ATCAGGCTGC CATGCAGATG
CTGAAGGAGA CCATCAATGA GGAGGCTGCT GAGTGGGACA GGCTGCATCC TGTGCACGCT
GGCCCCATTG CCCCCGGCCA GATGAGGGAG CCCAGGGGCT CTGACATTGC TGGCACCACC
TCCACCTCC AGGAGCAGAT TGGCTGGATG ACCAACAACC CCCCATCCC TGTGGGGGAA
ATCTACAAGA GGTGGATCAT CCTGGGCCTG AACAAGATTG TGAGGATGTA CTCCCCCACC
TCCATCCTGG ACATCAGGCA GGGCCCCAAG GAGCCCTTCA GGGACTATGT GGACAGGTC
TACAAGACC TGAGGGCTGA GCAGGCCTCC CAGGAGGTGA AGAACTGGAT GACAGAGACC
CTGCTGGTGC AGAATGCCAA CCCTGACTGC AAGACCATCC TGAAGGCCCT GGGCCCTGCT
GCCACCCTGG AGGAGATGAT GACAGCCTGC CAGGGGGTGG GGGGCCCTGG TCACAAGGCC
AGGGTGTGG CTGAGGCCAT GTCCCAGGTG ACCAACTCCG CCACCATCAT GATGCAGAGG
GGCAACTTCA GGAACCAGAG GAAGACAGTG AAGTGCTTCA ACTGTGGCAA GGTGGGCCAC
ATTGCCAAGA ACTGTAGGGC CCCCAGGAAG AAGGGCTGCT GGAAGTGTGG CAAGGAGGGC
CACCAGATGA AGGACTGCAA TGAGAGGCAG GCCAACTTCC TGGGCAAAAT CTGGCCCTCC
CACAAGGGCA GGCTGGCAA CTTCCTCCAG TCCAGGCCTG AGCCACAGC CCCTCCCGAG
GAGTCTTCA GGTTTGGGGA GGAGAAGACC ACCCCAGCC AGAAGCAGGA GCCCATTGAC
AAGGAGCTGT ACCCCCTGGC CTCCCTGAGG TCCCTGTTTG GCAACGACCC CTCTCCCGAG
ATGGCTCCCA TCTCCCCAT TGAGACTGTG CCTGTGAAGC TGAAGCCTGG CATGGATGGC
CCCAAGGTGA AGCAGTGGCC CCTGACTGAG GAGAAGATCA AGGCCCTGGT GGAAATCTGC
ACTGAGATGG AGAAGGAGGG CAAAATCTCC AAGATTGGCC CCGAGAACCC CTACAACACC
CCTGTGTTTG CCATCAAGAA GAAGGACTCC ACCAAGTGA GGAAGCTGGT GGACTTCAGG
GAGCTGAACA AGAGGACCCA GGACTTCTGG GAGGTGCAGC TGGGCATCCC CCACCCCGCT
GGCCTGAAGA AGAAGAAGTC TGTGACTGTG CTGGCTGTGG GGGATGCCTA CTTCTCTGTG
CCCCTGATG AGGACTTCAG GAAGTACACT GCCTTCACCA TCCCCTCCAT CAACAATGAG
ACCCCTGGCA TCAGGTACCA GTACAATGTG CTGCCCCAGG GCTGGAAGGG CTCCCCTGCC
ATCTTCCAGT CCTCCATGAC CAAGATCCTG GAGCCCTTCA GGAAGCAGAA CCCTGACATT
GTGATCTACC AGTACATGGC TGCCCTGTAT GTGGGCTCTG ACCTGGAGAT TGGGCAGCAC
AGGACCAAGA TTGAGGAGCT GAGGCAGCAC CTGCTGAGGT GGGGCCTGAC CACCCCTGAC
AAGAAGCACC AGAAGGAGCC CCCCTTCTG TGGATGGCT ATGAGCTGCA CCCCACAAG
TGGACTGTGC AGCCCATTTG GCTGCCTGAG AAGGACTCCT GGACTGTGAA TGACATCCAG
AAGCTGGTGG GCAAGCTGAA CTGGGCCTCC CAAATCTACC CTGGCATCAA GGTGAGGCAG
CTGTGCAAGC TGCTGAGGGG CACCAAGGCC CTGACTGAGG TGATCCCCCT GACTGAGGAG
GCTGAGCTGG AGCTGGCTGA GAACAGGGAG ATCCTGAAGG AGCCTGTGCA TGGGGTGTAC

FIGURE 33B

TATGACCCCT CCAAGGACCT GATTGCTGAG ATCCAGAAGC AGGGCCAGGG CCAGTGGACC
TACCAAATCT ACCAGGAGCC CTTCAAGAAC CTGAAGACTG GCAAGTATGC CAGGATGAGG
GGGGCCCA CAATGATGT GAAGCAGCTG ACTGAGGCTG TGCAGAAGAT CACCACTGAG
TCCATTGTGA TCTGGGGCAA GACCCCAAG TTCAAGCTGC CCATCCAGAA GGAGACCTGG
GAGACCTGGT GGA CTGAGTA CTGGCAGGCC ACCTGGATCC CTGAGTGGGA GTTTGTGAAC
ACCCCCCCC TGGTGAAGCT GTGGTACCAG CTGGAGAAGG AGCCCATTTGT GGGGGCTGAG
ACCTTCTATG TGGCTGGGGC TGCCAACAGG GAGACCAAGC TGGGCAAGGC TGGCTATGTG
ACCAACAGGG GCAGGCAGAA GGTGGTGACC CTGACTGACA CCACCAACCA GAAGACTGCC
CTCCAGGCCA TCTACCTGGC CCTCCAGGAC TCTGGCCTGG AGGTGAACAT TGTGACTGCC
TCCCAGTATG CCCTGGGCAT CATCCAGGCC CAGCCTGATC AGTCTGAGTC TGAGCTGGTG
AACCAGATCA TTGAGCAGCT GATCAAGAAG GAGAAGGTGT ACCTGGCCTG GGTGCCTGCC
CACAAGGGCA TTGGGGGCAA TGAGCAGGTG GACAAGCTGG TGTCTGCTGG CATCAGGAAG
GTGCTGTTCC TGGATGGCAT TGACAAGGCC CAGGATGAGC ATGAGAAGTA CCACTCCAAC
TGGAGGGCTA TGGCCTCTGA CTTCAACCTG CCCCTGTGG TGGCTAAGGA GATTGTGGCC
TCCTGTGACA AGTGCCAGCT GAAGGGGGAG GCCATGCATG GGCAGGTGGA CTGCTCCCCT
GGCATCTGGC AGCTGGCCTG CACCCACCTG GAGGGCAAGG TGATCCTGGT GGCTGTGCAT
GTGGCCTCCG GCTACATTGA GGCTGAGGTG ATCCCTGCTG AGACAGGCCA GGAGACTGCC
TACTTCCTGC TGAAGCTGGC TGGCAGGTGG CCTGTGAAGA CCATCCACAC TGCCAATGGC
TCCAACCTCA CTGGGGCCAC AGTGAGGGCT GCCTGCTGGT GGGCTGGCAT CAAGCAGGAG
TTTGGCATCC CCTACAACCC CCAGTCCCAG GGGGTGGTGG CCTCCATGAA CAAGGAGCTG
AAGAAGATCA TTGGGCAGGT GAGGGACCAG GCTGAGCACC TGAAGACAGC TGTGCAGATG
GCTGTGTTCA TCCACAACCT CAAGAGGAAG GGGGGCATCG GGGGCTACTC CGCTGGGGAG
AGGATTGTGG ACATCATTGC CACAGACATC CAGACCAAGG AGCTCCAGAA GCAGATCACC
AAGATCCAGA ACTTCAGGGT GTACTACAGG GACTCCAGGA ACCCCCTGTG GAAGGGCCCT
GCCAAGCTGC TGTGGAAGGG GGAGGGGGCT GTGGTGATCC AGGACAACTC TGACATCAAG
GTGGTGCCCA GGAGGAAGGC CAAGATCATC AGGGACTATG GCAAGCAGAT GGCTGGGGAT
GACTGTGTGG CCTCCAGGCA GGATGAGGAC TAA

SEQ ID NO: 38

FIGURE 34A

Met Gly Ala Arg Ala Ser Val Leu Ser Gly Gly Glu Leu Asp Lys Trp Glu Lys
 Ile Arg Leu Arg Pro Gly Gly Lys Lys Lys Tyr Lys Leu Lys His Ile Val Trp
 Ala Ser Arg Glu Leu Glu Arg Phe Ala Val Asn Pro Gly Leu Leu Glu Thr Ser
 Glu Gly Cys Arg Gln Ile Leu Gly Gln Leu Gln Pro Ser Leu Gln Thr Gly Ser
 Glu Glu Leu Arg Ser Leu Tyr Asn Thr Val Ala Thr Leu Tyr Cys Val His Gln
 Lys Ile Asp Val Lys Asp Thr Lys Glu Ala Leu Glu Lys Ile Glu Glu Glu Gln
 Asn Lys Ser Lys Lys Lys Ala Gln Gln Ala Ala Ala Gly Thr Gly Asn Ser Ser
 Gln Val Ser Gln Asn Tyr Pro Ile Val Gln Asn Leu Gln Gly Gln Met Val His
 Gln Ala Ile Ser Pro Arg Thr Leu Asn Ala Trp Val Lys Val Val Glu Glu Lys
 Ala Phe Ser Pro Glu Val Ile Pro Met Phe Ser Ala Leu Ser Glu Gly Ala Thr
 Pro Gln Asp Leu Asn Thr Met Leu Asn Thr Val Gly Gly His Gln Ala Ala Met
 Gln Met Leu Lys Glu Thr Ile Asn Glu Glu Ala Ala Glu Trp Asp Arg Leu His
 Pro Val His Ala Gly Pro Ile Ala Pro Gly Gln Met Arg Glu Pro Arg Gly Ser
 Asp Ile Ala Gly Thr Thr Ser Thr Leu Gln Glu Gln Ile Gly Trp Met Thr Asn
 Asn Pro Pro Ile Pro Val Gly Glu Ile Tyr Lys Arg Trp Ile Ile Leu Gly Leu
 Asn Lys Ile Val Arg Met Tyr Ser Pro Thr Ser Ile Leu Asp Ile Arg Gln Gly
 Pro Lys Glu Pro Phe Arg Asp Tyr Val Asp Arg Phe Tyr Lys Thr Leu Arg Ala
 Glu Gln Ala Ser Gln Glu Val Lys Asn Trp Met Thr Glu Thr Leu Leu Val Gln
 Asn Ala Asn Pro Asp Cys Lys Thr Ile Leu Lys Ala Leu Gly Pro Ala Ala Thr
 Leu Glu Glu Met Met Thr Ala Cys Gln Gly Val Gly Gly Pro Gly His Lys Ala
 Arg Val Leu Ala Glu Ala Met Ser Gln Val Thr Asn Ser Ala Thr Ile Met Met
 Gln Arg Gly Asn Phe Arg Asn Gln Arg Lys Thr Val Lys Cys Phe Asn Cys Gly
 Lys Val Gly His Ile Ala Lys Asn Cys Arg Ala Pro Arg Lys Lys Gly Cys Trp
 Lys Cys Gly Lys Glu Gly His Gln Met Lys Asp Cys Asn Glu Arg Gln Ala Asn
 Phe Leu Gly Lys Ile Trp Pro Ser His Lys Gly Arg Pro Gly Asn Phe Leu Gln
 Ser Arg Pro Glu Pro Thr Ala Pro Pro Glu Glu Ser Phe Arg Phe Gly Glu Glu
 Lys Thr Thr Pro Ser Gln Lys Gln Glu Pro Ile Asp Lys Glu Leu Tyr Pro Leu
 Ala Ser Leu Arg Ser Leu Phe Gly Asn Asp Pro Ser Ser Gln Met Ala Pro Ile
 Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys Pro Gly Met Asp Gly Pro Lys
 Val Lys Gln Trp Pro Leu Thr Glu Glu Lys Ile Lys Ala Leu Val Glu Ile Cys
 Thr Glu Met Glu Lys Glu Gly Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr
 Asn Thr Pro Val Phe Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu
 Val Asp Phe Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu
 Gly Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu Ala
 Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg Lys Tyr Thr
 Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile Arg Tyr Gln Tyr
 Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala Ile Phe Gln Ser Ser Met
 Thr Lys Ile Leu Glu Pro Phe Arg Lys Gln Asn Pro Asp Ile Val Ile Tyr Gln
 Tyr Met Ala Ala Leu Tyr Val Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr
 Lys Ile Glu Glu Leu Arg Gln His Leu Leu Arg Trp Gly Leu Thr Thr Pro Asp
 Lys Lys His Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro

FIGURE 34B

Asp Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr Val
Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln Ile Tyr Pro
Gly Ile Lys Val Arg Gln Leu Cys Lys Leu Leu Arg Gly Thr Lys Ala Leu Thr
Glu Val Ile Pro Leu Thr Glu Glu Ala Glu Leu Glu Leu Ala Glu Asn Arg Glu
Ile Leu Lys Glu Pro Val His Gly Val Tyr Tyr Asp Pro Ser Lys Asp Leu Ile
Ala Glu Ile Gln Lys Gln Gly Gln Gly Gln Trp Thr Tyr Gln Ile Tyr Gln Glu
Pro Phe Lys Asn Leu Lys Thr Gly Lys Tyr Ala Arg Met Arg Gly Ala His Thr
Asn Asp Val Lys Gln Leu Thr Glu Ala Val Gln Lys Ile Thr Thr Glu Ser Ile
Val Ile Trp Gly Lys Thr Pro Lys Phe Lys Leu Pro Ile Gln Lys Glu Thr Trp
Glu Thr Trp Trp Thr Glu Tyr Trp Gln Ala Thr Trp Ile Pro Glu Trp Glu Phe
Val Asn Thr Pro Pro Leu Val Lys Leu Trp Tyr Gln Leu Glu Lys Glu Pro Ile
Val Gly Ala Glu Thr Phe Tyr Val Ala Gly Ala Ala Asn Arg Glu Thr Lys Leu
Gly Lys Ala Gly Tyr Val Thr Asn Arg Gly Arg Gln Lys Val Val Thr Leu Thr
Asp Thr Thr Asn Gln Lys Thr Ala Leu Gln Ala Ile Tyr Leu Ala Leu Gln Asp
Ser Gly Leu Glu Val Asn Ile Val Thr Ala Ser Gln Tyr Ala Leu Gly Ile Ile
Gln Ala Gln Pro Asp Gln Ser Glu Ser Glu Leu Val Asn Gln Ile Ile Glu Gln
Leu Ile Lys Lys Glu Lys Val Tyr Leu Ala Trp Val Pro Ala His Lys Gly Ile
Gly Gly Asn Glu Gln Val Asp Lys Leu Val Ser Ala Gly Ile Arg Lys Val Leu
Phe Leu Asp Gly Ile Asp Lys Ala Gln Asp Glu His Glu Lys Tyr His Ser Asn
Trp Arg Ala Met Ala Ser Asp Phe Asn Leu Pro Pro Val Val Ala Lys Glu Ile
Val Ala Ser Cys Asp Lys Cys Gln Leu Lys Gly Glu Ala Met His Gly Gln Val
Asp Cys Ser Pro Gly Ile Trp Gln Leu Ala Cys Thr His Leu Glu Gly Lys Val
Ile Leu Val Ala Val His Val Ala Ser Gly Tyr Ile Glu Ala Glu Val Ile Pro
Ala Glu Thr Gly Gln Glu Thr Ala Tyr Phe Leu Leu Lys Leu Ala Gly Arg Trp
Pro Val Lys Thr Ile His Thr Ala Asn Gly Ser Asn Phe Thr Gly Ala Thr Val
Arg Ala Ala Cys Trp Trp Ala Gly Ile Lys Gln Glu Phe Gly Ile Pro Tyr Asn
Pro Gln Ser Gln Gly Val Val Ala Ser Met Asn Lys Glu Leu Lys Lys Ile Ile
Gly Gln Val Arg Asp Gln Ala Glu His Leu Lys Thr Ala Val Gln Met Ala Val
Phe Ile His Asn Phe Lys Arg Lys Gly Gly Ile Gly Gly Tyr Ser Ala Gly Glu
Arg Ile Val Asp Ile Ile Ala Thr Asp Ile Gln Thr Lys Glu Leu Gln Lys Gln
Ile Thr Lys Ile Gln Asn Phe Arg Val Tyr Tyr Arg Asp Ser Arg Asn Pro Leu
Trp Lys Gly Pro Ala Lys Leu Leu Trp Lys Gly Glu Gly Ala Val Val Ile Gln
Asp Asn Ser Asp Ile Lys Val Val Pro Arg Arg Lys Ala Lys Ile Ile Arg Asp
Tyr Gly Lys Gln Met Ala Gly Asp Asp Cys Val Ala Ser Arg Gln Asp Glu Asp

SEQ ID NO: 39

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 15/86

US CL : 435/456

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/205.1, 207.1, 227.1, 233.1; 435/69.1, 69.3, 173.3, 235.1, 320.1, 456; 530/23.72;

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	WO 96/39178 (ERTL et al.) 12 December 1996 (12.12.1996), see page 5, 6, 10, 12, 13 and claims 1 and 5.	1-3, 8-11, 18 — 4, 5, 13-17, 29-32, 34, 35, 37
X — Y	US 6,019,978 A (ERTL et al.) 1 February 2000, (01/02/2000), see columns 2, 7 and 8.	1-3, 8-11, 18 — 4, 5, 13-17, 29-32, 34, 35, 37
X,P	US 6,287,571 <i>B1</i> (ERTL et al.) 11 September 2001 (11/09/2001), see columns 2, 7, 8 and claim 1.	1, 9, 18
X — Y	US 5,643,579A (HUNG et al.) 1 July 1997 (01/07/1997), see examples 1, 2, 25 and 26.	1-3, 8, 9-11, 18 — 4,5,13-17, 29-32, 34, 35, 37
Y	WANG et al. The use of an E1-deleted, replication -defective adenovirus recombinant expressing the rabies virus glycoprotein for early vaccination of mice against rabies virus. Journal of Virology (March 1997) Vol. 71, No. 5, pp 3677-3683.	1-3, 9-11, 13-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	*X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent published on or after the international filing date	*Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*&	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

06 February 2002 (06.02.2002)

Date of mailing of the international search report

19 AUG 2002

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/28861

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NATUK et al. Immunogenicity of recombinant human adenovirus -human immunodeficiency virus vaccines in chimpanzees. Aids Research and Human Retroviruses (1993) Vol. 9, No. 5, pp395-404, see material and methods.	1, 9, 29-32
Y	PREVEC et al. Immune response to HIV-1 gag antigens induced by recombinant adenovirus vectors in mice and rhesus macaque monkeys. Journal of Acquired Immune Deficiency Syndrome. (1991) Vol. 4, No. 6 pp. 568-76, see abstract.	1, 9, 29-32
Y	LORI et al. Rapid protection against human immunodeficiency virus type 1 (HIV-1) replication mediated by high efficiency non-retroviral delivery of genes interfering with HIV-1 tat and gag. Gene Therapy (1994) Vol. 1, No. 1, pp. 27-31, see abstract.	1, 9
Y	PFARR et al. Differential effects of polyadenylation regions on gene expression in mammalian cells. DNA (1986) Vol. 5, No. 2, pp.115-22, see abstract.	16
Y	NATUK et al. Adenovirus vectored vaccine. Developmental Biological Standards (1994) Vol. 82, pp. 71-77, see abstract.	1, 9

INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-5, 8-11, 13-18, 29-32, 34, 35, 37

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group	Claims	
1	1-5, 8-11, 13-18, 29, 30, 31, 32, 34, 35, 37	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Gag protein (SEQ ID NO: 29)</u> inserted in the <u>parallel orientation of E1</u> . In addition the vector contains a promoter and a polyadenylation signal.
2	6, 7, 36	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> and <u>ΔE3</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Gag protein (SEQ ID NO: 29).
3	12, 33	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV protein inserted in the <u>antiparallel orientation of E1</u> .
4	19-23, 38-42	The claims are directed to a method of making and harvesting of a recombinant adenoviral particle that contains a gene encoding an HIV Gag protein.
5	24, 27, 28, 43, 46, 47	The claim is directed to a method of generating a cellular mediated immune response to HIV Gag protein with the recombinant adenoviral particle.
6	25, 26, 44, 45	The claim is directed to a method of generating a cellular mediated immune response to HIV Gag protein with the recombinant adenoviral particle in <u>addition to</u> administering a DNA plasmid vaccine.
7	48-51, 53, 54, 56	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 1)</u> inserted in the <u>parallel orientation of E1</u> .
8	48-51, 53, 54, 56	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 5)</u> inserted in the <u>parallel orientation of E1</u> .
9	48-51, 53, 54, 56	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 7)</u> inserted in the <u>parallel orientation of E1</u> .
10	52	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 1)</u> inserted in the <u>antiparallel orientation of E1</u> .
11	52	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 5)</u> inserted in the <u>antiparallel orientation of E1</u> .
12	52	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 7)</u> inserted in the <u>antiparallel orientation of E1</u> .
13	55	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u>

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		and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 1) inserted in E1.
14	55	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 5) inserted in E1.
15	55	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 7) inserted in E1.
16	57-61	The claims are directed to a method of making and harvesting of a recombinant adenoviral particle that contains a gene encoding an HIV Pol protein.
17	62, 65, 66	The claim is directed to a method of generating a cellular mediated immune response to HIV Pol protein with the recombinant adenoviral particle.
18	63, 64	The claim is directed to a method of generating a cellular mediated immune response to HIV Pol protein with the recombinant adenoviral particle in addition to administering a DNA plasmid vaccine.
19	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 9) inserted in the parallel orientation of E1.
20	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 11) inserted in the parallel orientation of E1.
21	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 13) inserted in the parallel orientation of E1.
22	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 15) inserted in the parallel orientation of E1.
23	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 9) inserted in the antiparallel orientation of E1.
24	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 11) inserted in the antiparallel orientation of E1.
25	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 13) inserted in the antiparallel orientation of E1.
26	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 15) inserted in the antiparallel orientation of E1.
27	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 9) inserted in E1.
28	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 11) inserted in E1.
29	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type

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		adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 13)</u> inserted in E1.
30	74	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> and <u>ΔE3</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 15)</u> inserted in E1.
31	76-80	The claims are directed to a method of making and harvesting of a recombinant adenoviral particle that contains a gene encoding an HIV Nef protein.
32	81, 84, 85	The claims are directed to a method of generating a cellular mediated immune response to HIV Nef with the recombinant adenoviral particle.
33	82, 83	The claims are directed to a method of generating a cellular mediated immune response to HIV Nef with the recombinant adenoviral particle <u>in addition to</u> administering a DNA plasmid vaccine.
34	86a	The claim is drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from three individual vectors.
35	86b, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from one individual vectors.
36	86c, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from two individual vectors, one expressing <i>nef-pol</i> fusion and one expressing <i>gag</i> .
37	86d, 87, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from two individual vectors, one expressing <i>gag-pol</i> fusion and one expressing <i>nef</i> .
38	86e, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from two individual vectors, one expressing <i>nef-gag</i> fusion and one expressing <i>pol</i> .
39	86f, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from a single vectors as a fusion protein.
40	86g, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> and <i>pol</i> are expressed from two individual vectors.
41	86h, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>gag</i> and <i>pol</i> are expressed individually from one vector.
42	86i, 88	The claims are drawn to a multivalent vaccine wherein <i>pol</i> and <i>nef</i> are expressed from two individual vectors.
43	86j, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>pol</i> and <i>nef</i> are expressed from individually from one vector.
44	86k, 88	The claims are drawn to a multivalent vaccine wherein <i>nef</i> and <i>gag</i> are expressed individually from one vector.
45	86l, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>nef</i> and <i>gag</i> are expressed individually from one vector.
46	86m, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> and <i>pol</i> are expressed as a fusion protein from one vector.
47	86n, 88	The claims are drawn to a multivalent vaccine wherein <i>pol</i> and <i>nef</i> are expressed as a fusion protein from one vector.
48	86o, 88	The claims are drawn to a multivalent vaccine wherein <i>nef</i> and <i>gag</i> are expressed as a fusion protein from one vector.

The inventions listed as Groups 1-48 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking groups 1-33 appears to be a recombinant adenoviral vector wherein the adenoviral vector is at least partially deleted in E1 but the vector may contain more deletions, the vector contains wild type sequences including packaging signals and a gene encoding a heterologous HIV protein or fragments thereof. Erdl et al. (WO 96/39178) disclose a recombinant adenoviral vector that is deleted in E1 and partially deleted in E3, the remainder of the adenoviral vector contains wild type sequences. The vector additionally contains an insertion of a heterologous protein which includes HIV proteins (see abstract and claims 1 and 5). Therefore, the technical feature linking the inventions of groups 1-45 does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The special technical feature of the following groups 1-3, 7-15, 19-30 and 34-48 is considered to be the combination of sequences that is disclosed in each group, see individual claim groupings above for the different sequences. The DNA disclosed in each group is made up of a different sequence having a different structure and different function.

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The special technical feature of group 4, 16 and 31 is considered to be a method of producing recombinant adenoviral particles. Each group contains different sequences hence the resulting particles would have different structures and functions associated with the particle.

The special technical feature of group 5, 17 and 32 is considered to be a method of producing a cellular mediated immune response to the heterologous protein encoded by the different adenoviral vectors. Each group contains different sequences a encoding different protein, therefore the resulting immune response will also be different.

The special technical feature of group 6, 18 and 33 is considered to be a method of producing a cellular mediated immune response to the heterologous protein encoded by the different adenoviral vectors in conjunction with immunizing the individual a DNA plasmid vaccine. Each method contains different sequences encoding a different protein, therefore the resulting immune response will also be different.

Accordingly, groups 1-48 are not so linked by the same or corresponding technical feature as to form a single general inventive concept.

Continuation of B. FIELDS SEARCHED Item 3:

WEST 2.0, STN-BIOSIS, MEDLINE

adenoviral vector, deletion, HIV, Gag, polyadenylation signal, CMV promoter

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